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(54) Title: TUMOR MARKERS IN OVARIAN CANCER

(57) Abstract: The present invention features methods of diagnosing and prognosticating ovarian tumors by detecting increased expression of an ovarian tumor marker gene in a subject or in a sample from a subject. Also featured are kits for the aforementioned diagnostic and prognostic methods. In addition, the invention features methods of treating and preventing ovarian tumors, and methods of inhibiting the growth or metastasis of ovarian tumors, by modulating the production or activity of an ovarian tumor marker polypeptide. Further featured are methods of inhibiting the growth or metastasis of an ovarian tumor by contacting an ovarian tumor cell with an antibody that specifically binds an ovarian tumor marker polypeptide.

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TUMOR MARKERS IN OVARIAN CANCER

This invention was made with intramural support from the National Institutes of Health. The government has certain rights in the invention.

FIELD OF THE INVENTION

This invention relates generally to the identification of ovarian tumor markers and diagnostic, prognostic, and therapeutic methods for their use, as well as kits for use in the aforementioned methods.

BACKGROUND OF THE INVENTION

Ovarian cancer is one of the most common forms of neoplasia in women. Early diagnosis and treatment of any cancer ordinarily improves the likelihood of survival. However, ovarian cancer is difficult to detect in its early stages, and remains the leading cause of death among women with cancer of the female reproductive tract.

The low survival rate of ovarian cancer patients is in part due to the lack of good diagnostic markers for the detection of early stage neoplasms, and in part due to a deficit in the general understanding of ovarian cancer biology, which would facilitate the development of effective anti-tumor therapies. The present invention overcomes these shortcomings by providing much-needed improvements for the diagnosis, treatment, and prevention ovarian tumors, based on the identification of a series of ovarian tumor marker genes that are highly expressed in ovarian epithelial tumor cells and are minimally expressed in normal ovarian epithelial cells. Over 75% of all ovarian tumors, and about 95% of all malignant ovarian tumors, arise from the ovarian surface epithelium (OSE). Because the tumor marker genes are broadly expressed in various types of ovarian epithelial tumors, the present invention should greatly improve the diagnosis and treatment of most ovarian cancers.

SUMMARY OF THE INVENTION

In a first aspect, the invention features a method of detecting an ovarian tumor in a subject. The method includes the step of measuring the expression level of an

ovarian tumor marker gene in the subject, wherein an increase in the expression level of the ovarian tumor marker gene in the subject, relative to the expression level of the ovarian tumor marker gene in a reference subject not having an ovarian tumor, detects an ovarian tumor in the subject.

In a second aspect, the invention features a method of identifying a subject at increased risk for developing ovarian cancer. The method includes the step of measuring the expression level of an ovarian tumor marker gene in the subject, wherein an increase in the expression level of the ovarian tumor marker gene in the subject, relative to the expression level of the ovarian tumor marker gene in a reference subject not at increased risk for developing ovarian cancer, identifies an individual at increased risk for developing ovarian cancer.

In a preferred embodiment of the second aspect of the invention, the expression level of the ovarian tumor marker gene in the subject is compared to the expression level of the tumor marker gene in a reference subject that is identified as having an increased risk for developing ovarian cancer.

In a third aspect, the invention features a method of determining the effectiveness of an ovarian cancer treatment in a subject. The method includes the step of measuring the expression level of an ovarian tumor marker gene in the subject after treatment of the subject, wherein a modulation in the expression level of the ovarian tumor marker gene in the subject, relative to the expression level of the ovarian tumor marker gene in the subject prior to treatment, indicates an effective ovarian cancer treatment in the subject.

In a preferred embodiment of the first three aspects of the invention, the expression level of the ovarian tumor marker gene is determined in the subject by measuring the expression level of the tumor marker gene in a sample from the subject. The sample may be, for example, a tissue biopsy, ovarian epithelial cell scrapings, peritoneal fluid, blood, urine, or serum. In another preferred embodiment of the first three aspects of the invention, the expression level of the tumor marker gene is measured *in vivo* in the subject.

In yet another preferred embodiment of the first three aspects of the invention, the expression level of more than one ovarian tumor marker gene is measured. For

example, the expression level of two, three, four, five, or more tumor marker genes may be measured.

In various other embodiments of the first three aspects of the invention, the expression level of the tumor marker gene may be determined by measuring the level of ovarian tumor marker mRNA. For example, the level of ovarian tumor marker mRNA may be measured using RT-PCR, Northern hybridization, dot-blotting, or *in situ* hybridization. In addition, or alternatively, the expression level of the ovarian tumor marker gene may be determined by measuring the level of ovarian tumor marker polypeptide encoded by the ovarian tumor marker gene. For example, the level of ovarian tumor marker polypeptide may be measured by ELISA, immunoblotting, or immunohistochemistry. The level of ovarian tumor marker polypeptide may also be measured *in vivo* in the subject using an antibody that specifically binds an ovarian tumor marker polypeptide, coupled to a paramagnetic label or other label used for *in vivo* imaging, and visualizing the distribution of the labeled antibody within the subject using an appropriate *in vivo* imaging method, such as magnetic resonance imaging.

In still another embodiment of the first three aspects of the invention, the expression level of the tumor marker gene may be compared to the expression level of the tumor marker gene in a reference subject diagnosed with ovarian cancer.

In a fourth aspect, the invention features a method of identifying a tumor as an ovarian tumor. The method includes the step of measuring the expression level of an ovarian tumor marker gene in a tumor cell from the tumor, wherein an increase in the expression level of the ovarian tumor marker gene in the tumor cell, relative to the expression level of the ovarian tumor marker gene in a noncancerous ovarian cell, identifies the tumor as an ovarian tumor.

In a fifth aspect, the invention features a method of treating or preventing an ovarian tumor in a subject. The method includes the step of modulating production or activity of a polypeptide encoded by an ovarian tumor marker gene in an ovarian epithelial cell in the subject.

In a sixth aspect, the invention features a method of inhibiting the growth or metastasis of an ovarian tumor cell in a subject. The method includes the step of

modulating production or activity of a polypeptide encoded by an ovarian tumor marker gene in the ovarian tumor cell in the subject.

In a seventh aspect, the invention features a method of inhibiting the growth or metastasis of an ovarian tumor in a subject. The method includes the step of contacting an ovarian tumor cell with an antibody that specifically binds an ovarian tumor marker polypeptide encoded by an ovarian tumor marker gene, wherein the binding of the antibody to the ovarian tumor marker polypeptide inhibits the growth or metastasis of the ovarian tumor in the subject.

In various preferred embodiments of the seventh aspect of the invention, the ovarian tumor marker polypeptide may be on the surface of the ovarian tumor cell, and the antibody may be coupled to a radioisotope or to a toxic compound.

In an eighth aspect, the invention features a kit including an antibody for measuring the expression level of an ovarian tumor marker gene in a subject.

In a ninth aspect, the invention features a kit including a nucleic acid for measuring the expression level of an ovarian tumor marker gene in a subject.

In a tenth aspect, the invention features a method of diagnosing ovarian cancer in a subject. The method includes the step of measuring the amount of an ovarian tumor marker polypeptide in the subject, wherein an amount of ovarian tumor marker polypeptide that is greater than the amount of ovarian tumor marker polypeptide measured in a subject not having ovarian cancer diagnoses an ovarian cancer in the subject.

In various embodiments of the tenth aspect of the invention, the ovarian tumor marker polypeptide can be present at the surface of a cell (e.g., a cell-surface-localized polypeptide such as a cell adhesion molecule), or the ovarian tumor marker polypeptide may be in soluble form (e.g., secreted from a cell, released from a lysed cell, or otherwise detectable in a fluid-based assay).

In a preferred embodiment of all of the above aspects of the invention, the ovarian tumor may be an epithelial ovarian tumor. The epithelial ovarian tumor may be, for example, a serous cystadenoma, a borderline serous tumor, a serous cystadenocarcinoma, a mucinous cystadenoma, a borderline mucinous tumor, a mucinous cystadenocarcinoma, an endometrioid carcinoma, an undifferentiated

carcinoma, a cystadenofibroma, an adenofibroma, or a Brenner tumor. The epithelial ovarian tumor may also be a clear cell adenocarcinoma.

In preferred embodiments of all of the above aspects of the invention, the ovarian tumor marker gene can be, but is not limited to, alpha prothymosin; beta polypeptide 2-like G protein subunit 1; tumor rejection antigen-1 (gp96)1; HSP90; Hepatoma-Derived Growth Factor (HGDF); DKFZp5860031; CD63 antigen (melanoma 1 antigen); protein kinase C substrate 80K-H; Polymerase II cofactor 4 (PC4); mitochondrial Tu translation elongation factor; hNRP H1; Solute carrier family 2; KIAA0591 protein; X-ray repair protein; DKFZP564M2423 protein; growth factor-regulated tyrosine kinase substrate; and eIF-2-associated p67. The ovarian tumor marker gene may also be HSP60 or Lutheran blood group (B-CAM). In other preferred embodiments of all aspects of the invention, the ovarian tumor marker gene may also be HLA-DR alpha chain; cysteine-rich protein 1; claudin 4; claudin 3; ceruloplasmin (ferroxidase); glutathione perroxidase 3; secretory leukocyte protease inhibitor; HOST-1 (FLJ14303 fis); interferon-induced transmembrane protein 1; apolipoprotein J/clusterin; serine protease inhibitor, Kunitz type 2; apoplipoprotein E; complement component 1, r subcomponent; G1P3/IFI-6-16; Lutheran blood group (BCAM); collagen type III, alpha-1; Mal (T cell differentiation protein); collagen type I, alpha-2; HLA-DPB1; bone marrow stroma antigen 2 (BST-2); or HLA-Cw.

The ovarian tumor marker gene may also be HOST-3 (Claudin-16) (e.g., Genbank Accession No. XM_003150; SEQ ID NOs: 141 and 142); HOST-4 (e.g., a gene that comprises SEQ ID NO: 144); or HOST-5 (sodium dependent transporter isoform NaPi-Iib) (e.g., Genbank Accession No. AF146796; SEQ ID NOs: 146 and 147).

In other preferred embodiments of all aspects of the invention, the ovarian tumor marker gene comprises a nucleotide sequence set forth in one of SEQ ID NOs: 84-102.

In still other preferred embodiments of all aspects of the invention, the ovarian tumor marker gene comprises a nucleotide sequence set forth in one of SEQ ID NOs: 103-129.

In yet other preferred embodiments of all aspects of the invention, the ovarian tumor marker gene comprises a nucleotide sequence set forth in one of SEQ ID NOs: 141, 143, or 145.

Additional advantages of the invention will be set forth in part in the description which follows, and in part will be obvious from the description, or may be learned by practice of the invention. The advantages of the invention will be realized and attained by means of the elements and combinations particularly pointed out in the appended claims. It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the invention, as claimed.

DETAILED DESCRIPTION OF THE INVENTION

The low survival rate of ovarian cancer patients is in part due to the lack of good diagnostic markers allowing early detection of the disease. Further compounding this difficulty in early diagnosis is the lack of effective treatments for ovarian cancer, development of which has been impeded by a deficit in the general understanding of ovarian cancer biology. The present invention overcomes these deficits in the art by providing ovarian tumor markers that are expressed at elevated levels in ovarian epithelial tumor cells, relative to their expression in normal ovarian epithelial cells.

To identify marker genes that are up-regulated in ovarian tumor cells, SAGE (Serial Analysis of Gene Expression; Velculescu et al., *Science* 270:484-487, 1995) was employed to obtain global gene expression profiles of three ovarian tumors, five ovarian tumor cell lines of various histological types, a pool of ten ovarian tumor cell lines of various histological types, and normal human ovarian surface epithelium (HOSE). The expression patterns were generated by acquiring thousands of short sequence tags that contain sufficient information to uniquely identify transcripts due to the unique position of each tag within the transcript. Comparing the SAGE-generated expression profiles between ovarian cancer and HOSE revealed an abundance of genes that are expressed at elevated levels in ovarian tumor cells, relative to their expression in normal HOSE.

Selected SAGE results were further validated through immunohistochemical analysis of archival ovarian serous carcinoma samples. Ovarian tumor marker genes implicated in immune response pathways, regulation of cell proliferation, and protein folding were identified, many of which are membrane-localized or secreted. The ovarian tumor marker genes identified from these SAGE profiles are useful both as diagnostic and prognostic markers to detect and monitor a broad variety of ovarian cancers, and as therapeutic targets for the treatment of such ovarian cancers.

Definitions

In this specification and in the claims that follow, reference is made to a number of terms that shall be defined to have the following meanings.

As used in the specification and in the appended claims, the singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise. For example, "a cell" can mean a single cell or more than one cell.

By "ovarian cell" is meant a cell that is of ovarian origin or that is a descendent of a cell of ovarian origin (e.g., a metastatic tumor cell in the liver that is derived from a tumor originating in the ovary), irrespective of whether the cell is physically within the ovary at the time at which it is subjected to a diagnostic test or an anti-tumor treatment. For example, the ovarian cell may be a normal ovarian cell or an ovarian tumor cell, either within the ovary or at another location within the body. The ovarian cell may also be outside the body (for example, in a tissue biopsy). A preferred ovarian cell is an ovarian cell of epithelial origin.

By "ovarian tumor marker gene" is meant a gene of the invention, for which expression is increased (as described below) in ovarian tumor cells relative to normal ovarian cells. Preferably, an ovarian tumor marker gene has been observed to display increased expression in at least two ovarian tumor SAGE libraries (relative to a HOSE library), more preferably in at least three SAGE libraries, and most preferably in at least four SAGE libraries (relative to a HOSE library). Examples of ovarian tumor marker genes are provided in Tables 2 and 4 hereinbelow.

By "ovarian tumor marker polypeptide" is meant a polypeptide that is encoded by an ovarian tumor marker gene and is produced at an increased level in an ovarian

tumor cell due to the increased expression of the ovarian tumor marker gene that encodes the polypeptide.

By “sample” is meant any body fluid (e.g., but not limited to, blood, serum, urine, cerebrospinal fluid, semen, sputum, saliva, tears, joint fluids, body cavity fluids (e.g., peritoneal fluid), or washings), tissue, or organ obtained from a subject; a cell (either within a subject, taken directly from a subject, or a cell maintained in culture or from a cultured cell line); a lysate (or lysate fraction) or extract derived from a cell; or a molecule derived from a cell or cellular material.

By “modulate” is meant to alter, by increase or decrease.

By “increase in gene expression level,” “expressed at an increased level,” “increased expression,” and similar phrases is meant a rise in the relative amount of mRNA or protein, e.g., on account of an increase in transcription, translation, mRNA stability, or protein stability, such that the overall amount of a product of the gene, i.e., an mRNA or polypeptide, is augmented. Preferably the increase is by at least about 3-fold, more preferably, by at least about: 4-fold, 5-fold, 7-fold, 10-fold, 15-fold, 20-fold, 30-fold, 40-fold, 50-fold, 70-fold, or more. For example, as described herein, the expression level of the ovarian tumor marker genes of the invention is generally increased by at least 3-fold in ovarian tumor cells, relative to normal ovarian surface epithelial cells.

By “decrease in gene expression level” is meant a reduction in the relative amount of mRNA or protein transcription, translation, mRNA stability, or protein stability, such that the overall amount of a product of the gene, i.e., an mRNA or polypeptide, is reduced. Preferably the decrease is by at least about 20%-25%, more preferably by at least about 26%-50%, still more preferably by at least about 51%-75%, even more preferably by at least about 76%-95%, and most preferably, by about 96%-100%.

By “about” is meant ±10% of a recited value.

By “modulating production or activity of a polypeptide encoded by an ovarian tumor marker gene” is meant to increase or decrease gene expression level, as described above, or to stimulate or inhibit the ability of an ovarian tumor marker polypeptide to perform its intrinsic biological function (examples of such functions include, but are

not limited to, enzymatic activity, e.g., kinase activity or GTPase activity; cell-signaling activity, e.g., activation of a growth factor receptor; or cell adhesion activity. The modulation may be an increase in the amount of the polypeptide produced or an increase in the activity of the polypeptide, of at least about: 2-fold, 4-fold, 6-fold, or 10-fold, or the modulation may be a decrease in the amount of the polypeptide produced or a decrease in the activity of the polypeptide, of at least about: 20%-25%, 26%-50%, 51%-75%, 76%-95%, or 96%-100%. These increases and/or decreases are compared with the amount of production and/or activity in a normal cell, sample, or subject.

By "effective amount" of a compound as provided herein is meant a nontoxic but sufficient amount of the compound to provide the desired effect, e.g., modulation of ovarian tumor marker gene expression or modulation of ovarian tumor marker polypeptide activity. As will be pointed out below, the exact amount required will vary from subject to subject, depending on the species, age, and general condition of the subject, the severity and type of disease that is being treated, the particular compound used, its mode of administration, and the like. Thus, it is not possible to specify an exact "effective amount." However, an appropriate "effective amount" may be determined by one of ordinary skill in the art using only routine experimentation.

By "pharmaceutically acceptable" is meant a material that is not biologically or otherwise undesirable, i.e., the material may be administered to an individual along with a molecule or compound of the invention (e.g., an antibody or nucleic acid molecule) without causing any undesirable biological effects or interacting in a deleterious manner with any of the other components of the pharmaceutical composition in which it is contained.

By "having an increased risk" is meant a subject that is identified as having a higher than normal chance of developing an ovarian tumor, compared to the general population. Such subjects include, for example, women that have a hereditary disposition to develop ovarian cancer, for example, those identified as harboring one or more genetic mutations (e.g., a mutation in the BRCA-1 gene) that are known indicators of a greater than normal chance of developing ovarian cancer, or who have a familial history of ovarian cancer. In addition, a subject who has had, or who currently has, an ovarian tumor is a subject who has an increased risk for developing an ovarian

tumor, as such a subject may continue to develop new tumors. Subjects who currently have, or who have had, an ovarian tumor also have an increased risk for ovarian tumor metastases.

By "treat" is meant to administer a compound or molecule of the invention to a subject in order to: eliminate an ovarian tumor or reduce the size of an ovarian tumor or the number of ovarian tumors in a subject; arrest or slow the growth of an ovarian tumor in a subject; inhibit or slow the development of a new ovarian tumor or an ovarian tumor metastasis in a subject; or decrease the frequency or severity of symptoms and/or recurrences in a subject who currently has or who previously has had an ovarian tumor.

By "prevent" is meant to minimize the chance that a subject will develop an ovarian tumor or to delay the development of an ovarian tumor. For example, a woman at increased risk for an ovarian tumor, as described above, would be a candidate for therapy to prevent an ovarian tumor.

By "specifically binds" is meant that an antibody recognizes and physically interacts with its cognate antigen and does not significantly recognize and interact with other antigens.

By "probe," "primer," or "oligonucleotide" is meant a single-stranded DNA or RNA molecule of defined sequence that can base-pair to a second DNA or RNA molecule that contains a complementary sequence (the "target"). The stability of the resulting hybrid depends upon the extent of the base-pairing that occurs. The extent of base-pairing is affected by parameters such as the degree of complementarity between the probe and target molecules, and the degree of stringency of the hybridization conditions. The degree of hybridization stringency is affected by parameters such as temperature, salt concentration, and the concentration of organic molecules such as formamide, and is determined by methods known to one skilled in the art. Probes or primers specific for ovarian tumor marker nucleic acids (e.g., genes and/or mRNAs) preferably have at least 50%-55% sequence complementarity, more preferably at least 60%-75% sequence complementarity, even more preferably at least 80%-90% sequence complementarity, yet more preferably at least 91%-99% sequence complementarity, and most preferably 100% sequence complementarity to the ovarian

tumor marker nucleic acid to be detected. Probes, primers, and oligonucleotides may be detectably-labeled, either radioactively, or non-radioactively, by methods well-known to those skilled in the art. Probes, primers, and oligonucleotides are used for methods involving nucleic acid hybridization, such as: nucleic acid sequencing, reverse transcription and/or nucleic acid amplification by the polymerase chain reaction, single stranded conformational polymorphism (SSCP) analysis, restriction fragment polymorphism (RFLP) analysis, Southern hybridization, Northern hybridization, *in situ* hybridization, electrophoretic mobility shift assay (EMSA).

By "specifically hybridizes" is meant that a probe, primer, or oligonucleotide recognizes and physically interacts (i.e., base-pairs) with a substantially complementary nucleic acid (e.g., an ovarian tumor marker mRNA of the invention) under high stringency conditions, and does not substantially base pair with other nucleic acids.

By "high stringency conditions" is meant conditions that allow hybridization comparable with the hybridization that occurs using a DNA probe of at least 500 nucleotides in length, in a buffer containing 0.5 M $NaHPO_4$, pH 7.2, 7% SDS, 1 mM EDTA, and 1 % BSA (fraction V), at a temperature of 65° C, or a buffer containing 48% formamide, 4.8X SSC, 0.2 M Tris-Cl, pH 7.6, 1X Denhardt's solution, 10% dextran sulfate, and 0.1% SDS, at a temperature of 42° C (these are typical conditions for high stringency Northern or Southern hybridizations). High stringency hybridization is relied upon for the success of numerous techniques routinely performed by molecular biologists, such as high stringency PCR, DNA sequencing, single strand conformational polymorphism analysis, and *in situ* hybridization. In contrast to Northern and Southern hybridizations, these techniques are usually performed with relatively short probes (e.g., usually 16 nucleotides or longer for PCR or sequencing, and 40 nucleotides or longer for *in situ* hybridization). The high stringency conditions used in these techniques are well known to those skilled in the art of molecular biology, and may be found, for example, in F. Ausubel et al., *Current Protocols in Molecular Biology*, John Wiley & Sons, New York, NY, 1997, herein incorporated by reference.

Examples of ovarian tumor marker genes

Examples of ovarian tumor marker genes of the invention include alpha prothymosin (e.g., Genbank Accession No. M14483; SEQ ID NOs: 1 and 2); beta polypeptide 2-like G protein subunit 1 (e.g., Genbank Accession No. M24194; SEQ ID NOs: 3 and 4); tumor rejection antigen-1 (gp96)1 (e.g., Genbank Accession No. NM_003299; SEQ ID NOs: 7 and 8); HSP90 (e.g., Genbank Accession No. AA071048; SEQ ID NOs: 9 and 10); Hepatoma-Derived Growth Factor (HGDF) (e.g., Genbank Accession No. D16431; SEQ ID NOs: 13 and 14); DKFZp5860031 (e.g., Genbank Accession No. AL117237; SEQ ID NOs: 15 and 16); CD63 antigen (melanoma 1 antigen) (e.g., Genbank Accession No. AA041408; SEQ ID NOs: 17 and 18); protein kinase C substrate 80K-H (e.g., Genbank Accession No. J03075; SEQ ID NOs: 19 and 20); Polymerase II cofactor 4 (PC4) (e.g., Genbank Accession No. X79805; SEQ ID NOs: 21 and 22); mitochondrial Tu translation elongation factor (e.g., Genbank Accession No. L38995; SEQ ID NOs: 23 and 24); hNRP H1 (e.g., Genbank Accession No. L22009; SEQ ID NOs: 25 and 26); Solute carrier family 2 (e.g., Genbank Accession No. AF070544; SEQ ID NOs: 27 and 28); KIAA0591 protein (e.g., Genbank Accession No. AB011163; SEQ ID NOs: 29 and 30); X-ray repair protein (e.g., Genbank Accession No. AF035587; SEQ ID Nos: 31 and 32); DKFZP564M2423 protein (e.g., Genbank Accession No. BC003049; SEQ ID NOs: 35 and 139); growth factor-regulated tyrosine kinase substrate (e.g., Genbank Accession No. D84064; SEQ ID NOs: 36 and 37); and/or eIF-2-associated p67 (e.g., Genbank Accession No. U29607; SEQ ID NOs: 38 and 39). The ovarian tumor marker gene may also be HSP60 (e.g., Genbank Accession No. M22382; SEQ ID NOs: 11 and 12) and Lutheran blood group protein (B-CAM) (e.g., Genbank Accession No. NM_005581; SEQ ID NOs: 5 and 6).

Other examples of ovarian tumor marker genes of the invention include HLA-DR alpha chain (e.g., Genbank Accession No. K01171; SEQ ID NOs: 40 and 41); cysteine-rich protein 1 (e.g., Genbank Accession No. NM_001311; SEQ ID NOs: 42 and 43); claudin 4 (e.g., Genbank Accession No. NM_001305; SEQ ID NOs: 44 and 45); HOST-2 (e.g., SEQ ID NO: 46); claudin 3 (e.g., Genbank Accession No. NM_001306; SEQ ID NOs: 47 and 48); ceruloplasmin (ferroxidase) (e.g., Genbank

Accession No. M13699; SEQ ID NOs: 49 and 50); glutathione perroxidase 3 (e.g., Genbank Accession No. D00632; SEQ ID NOs: 51 and 52); secretory leukocyte protease inhibitor (e.g., Genbank Accession No. AF114471; SEQ ID NOs: 53 and 54); HOST-1 (FLJ14303 fis) (e.g., Genbank Accession No. AK024365; SEQ ID NOs: 55 and 56); interferon-induced transmembrane protein 1 (e.g., Genbank Accession No. J04164; SEQ ID NOs: 57 and 58); apolipoprotein J/clusterin (e.g., Genbank Accession No. J02908; SEQ ID NOs: 59 and 60); serine protease inhibitor, Kunitz type 2 (e.g., Genbank Accession No. AF027205; SEQ ID NOs: 61 and 62); apoplipoprotein E (e.g., Genbank Accession No. BC003557; SEQ ID NOs: 63 and 64); complement component 1, r subcomponent (e.g., Genbank Accession No. M14058; SEQ ID NOs: 65 and 66); G1P3/IFI-6-16 (e.g., Genbank Accession No. X02492; SEQ ID NOs: 67 and 68); Lutheran blood group (BCAM) (e.g., Genbank Accession No. X83425; SEQ ID NOs: 69 and 70); collagen type III, alpha-1 (e.g., Genbank Accession No. X14420; SEQ ID NOs: 71 and 72); Mal (T cell differentiation protein) (e.g., Genbank Accession No. M15800; SEQ ID NOs: 73 and 74); collagen type I, alpha-2 (e.g., Genbank Accession No. J03464; SEQ ID NOs: 75 and 76); HLA-DPB1 (e.g., Genbank Accession No. J03041; SEQ ID NOs: 77 and 78); bone marrow stroma antigen 2 (BST-2) (e.g., Genbank Accession No. D28137; SEQ ID NOs: 79 and 80); and HLA-Cw (e.g., Genbank Accession No. X17093; SEQ ID NOs: 81 and 82).

Still other examples of ovarian tumor marker genes of the invention include HOST-3 (Claudin-16) (e.g., Genbank Accession No. XM_003150; SEQ ID NOs: 141 and 142); HOST-4 (e.g., a gene that comprises SEQ ID NO: 144); or HOST-5 (sodium dependent transporter isoform NaPi-Iib) (e.g., Genbank Accession No. AF146796; SEQ ID NOs: 146 and 147).

Ovarian tumor marker genes of the invention may also be described by SAGE tags, as disclosed herein. For example, an ovarian tumor marker genes of the invention can include a nucleotide sequence set forth in one of SEQ ID NOs: 84-102; 103-129; or 141, 143, or 145.

Diagnostic uses of ovarian tumor marker genes and polypeptides

The ovarian tumor marker genes of the invention are overexpressed in a broad variety of ovarian epithelial tumor cells, relative to normal ovarian epithelial cells. This differential expression can be exploited in diagnostic tests for ovarian cancer, in prognostic tests for assessing the relative severity of ovarian cancer, in tests for monitoring a subject in remission from ovarian cancer, and in tests for monitoring disease status in a subject being treated for ovarian cancer. Increased expression of an ovarian tumor marker gene, i.e., detection of elevated levels of ovarian tumor marker mRNA and/or protein in a subject or in a sample from a subject (i.e., levels at least three-fold higher than in a normal subject or in an equivalent sample, e.g., blood, cells, or tissue from a normal subject) is diagnostic of ovarian cancer.

One of ordinary skill in the art will understand that in some instances, higher expression of a given ovarian tumor marker gene will indicate a worse prognosis for a subject having ovarian cancer. For example, relatively higher levels of ovarian tumor marker gene expression may indicate a relative large primary tumor, a higher tumor burden (e.g., more metastases), or a relatively more malignant tumor phenotype.

The diagnostic and prognostic methods of the invention involve using known methods, e.g., antibody-based methods to detect ovarian tumor marker polypeptides and nucleic acid hybridization- and/or amplification-based methods to detect ovarian tumor marker mRNA. One of ordinary skill in the art will understand how to choose the most appropriate method for measuring ovarian tumor marker expression, based upon the combination of the particular ovarian tumor marker to be measured, the information desired, and the particular type of diagnostic test to be used. For example, immunological tests such as enzyme-linked immunosorbent assays (ELISA), radioimmunoassays (RIA), and Western blots may be used to measure the level of an ovarian tumor marker polypeptide in a body fluid sample (such as blood, serum, sputum, urine, or peritoneal fluid). Biopsies, tissue samples, and cell samples (such as ovaries, lymph nodes, ovarian surface epithelial cell scrapings, lung biopsies, liver biopsies, and any fluid sample containing cells (such as peritoneal fluid, sputum, and pleural effusions) may be tested by disaggregating and/or solubilizing the tissue or cell sample and subjecting it to an immunoassay for polypeptide detection, such as ELISA,

RIA, or Western blotting. Such cell or tissue samples may also be analyzed by nucleic acid-based methods, e.g., reverse transcription-polymerase chain reaction (RT-PCR) amplification, Northern hybridization, or slot- or dot-blotting. To visualize the three-dimensional distribution of tumor cells within a tissue sample, diagnostic tests that preserve the tissue structure of a sample, e.g., immunohistological staining, *in situ* RNA hybridization, or *in situ* RT-PCR may be employed to detect ovarian tumor marker polypeptide or mRNA, respectively. For *in vivo* localization of tumor masses, imaging tests such as magnetic resonance imaging (MRI) may be employed by introducing into the subject an antibody that specifically binds an ovarian tumor marker polypeptide (particularly a cell surface-localized polypeptide), wherein the antibody is conjugated or otherwise coupled to a paramagnetic tracer (or other appropriate detectable moiety, depending upon the imaging method used); alternatively, localization of an unlabeled tumor marker-specific antibody may be detected using a secondary antibody coupled to a detectable moiety.

The skilled artisan will understand that selection of a particular ovarian tumor marker polypeptide as the target for detection in any diagnostic test and selection of the particular test to be employed will depend upon the type of sample to be tested. For example, measurement of ovarian tumor marker polypeptides that are secreted from a cell (e.g., HDGF) may be preferred for serological tests. Moreover, ovarian tumor marker polypeptides that are not normally actively secreted from cells (e.g., intracellular or membrane-associated polypeptides), but that are found in blood and other fluid samples (e.g., peritoneal fluid or washings) at detectable levels in subjects having tumors (e.g., due to tumor cell lysis) are considered to be soluble ovarian tumor marker polypeptides that may be used in serological and other diagnostic assays of body fluids.

A fluid sample (such as blood, peritoneal fluid, sputum, or pleural effusions) from a subject with ovarian cancer, particularly metastatic cancer, may contain one or more ovarian tumor cells or ovarian tumor cell fragments. The presence of such cells or fragments allows detection of a tumor mRNA using an RT-PCR assay, e.g., but not limited to, real-time quantitative RT-PCR using the Taqman method (Heid and Stevens, *Genome Res.* 6:986-94, 1996).

In addition, since rapid tumor cell destruction often results in autoantibody generation, the ovarian tumor markers of the invention may be used in serological assays (e.g., an ELISA test of a subject's serum) to detect autoantibodies against ovarian tumor markers in a subject. Ovarian tumor marker polypeptide-specific autoantibody levels that are at least about 3-fold higher (and preferably at least 5-fold or 7-fold higher, most preferably at least 10-fold or 20-fold higher) than in a control sample are indicative of ovarian cancer.

Cell-surface localized, intracellular, and secreted ovarian tumor marker polypeptides may all be employed for analysis of biopsies, e.g., tissue or cell samples (including cells obtained from liquid samples such as peritoneal cavity fluid) to identify a tissue or cell biopsy as containing ovarian tumor cells. A biopsy may be analyzed as an intact tissue or as a whole-cell sample, or the tissue or cell sample may be disaggregated and/or solubilized as necessary for the particular type of diagnostic test to be used. For example, biopsies or samples may be subjected to whole-tissue or whole-cell analysis of ovarian tumor marker polypeptide or mRNA levels *in situ*, e.g., using immunohistochemistry, *in situ* mRNA hybridization, or *in situ* RT-PCR. The skilled artisan will know how to process tissues or cells for analysis of polypeptide or mRNA levels using immunological methods such as ELISA, immunoblotting, or equivalent methods, or analysis of mRNA levels by nucleic acid-based analytical methods such as RT-PCR, Northern hybridization, or slot- or dot-blotting.

All of the above methods are well-known in the art. For example, generation of antibodies against a given protein, ELISA, immunoblotting, selection of nucleic acid primers for PCR, RT-PCR, Northern hybridization, *in situ* hybridization, *in situ* RT-PCR, and slot- or dot-blotting are all well-described in *Current Protocols in Molecular Biology* (Ausubel et al., eds.), John Wiley and Sons, Inc., 1996.

Kits for measuring expression levels of ovarian tumor marker genes

The present invention provides kits for detecting an increased expression level of an ovarian tumor marker gene in a subject. A kit for detecting ovarian tumor marker polypeptide will contain an antibody that specifically binds a chosen ovarian tumor marker polypeptide. A kit for detecting ovarian tumor marker mRNA will contain one

or more nucleic acids (e.g., one or more oligonucleotide primers or probes, DNA probes, RNA probes, or templates for generating RNA probes) that specifically hybridize with a chosen ovarian tumor marker mRNA.

Particularly, the antibody-based kit can be used to detect the presence of, and/or measure the level of, an ovarian tumor marker polypeptide that is specifically bound by the antibody or an immunoreactive fragment thereof. The kit can include an antibody reactive with the antigen and a reagent for detecting a reaction of the antibody with the antigen. Such a kit can be an ELISA kit and can contain a control (e.g., a specified amount of a particular ovarian tumor marker polypeptide), primary and secondary antibodies when appropriate, and any other necessary reagents such as detectable moieties, enzyme substrates and color reagents as described above. The diagnostic kit can, alternatively, be an immunoblot kit generally comprising the components and reagents described herein.

A nucleic acid-based kit can be used to detect and/or measure the expression level of an ovarian tumor marker gene by detecting and/or measuring the amount of ovarian tumor marker mRNA in a sample, such as a tissue or cell biopsy (e.g., an ovary, ovarian cell scrapings, a bone marrow biopsy, a lung biopsy or lung aspiration, etc.). For example, an RT-PCR kit for detection of elevated expression of an ovarian tumor marker gene will contain oligonucleotide primers sufficient to perform reverse transcription of ovarian tumor marker mRNA to cDNA and PCR amplification of ovarian tumor marker cDNA, and will preferably also contain control PCR template molecules and primers to perform appropriate negative and positive controls, and internal controls for quantitation. One of ordinary skill in the art will understand how to select the appropriate primers to perform the reverse transcription and PCR reactions, and the appropriate control reactions to be performed. Such guidance is found, for example, in F. Ausubel et al., *Current Protocols in Molecular Biology*, John Wiley & Sons, New York, NY, 1997. Numerous variations of RT-PCR are known in the art. One example of a quantitative RT-PCR assay is the real-time quantitative RT-PCR assay described by Heid and Stevens (*Genome Res.* 6:986-94, 1996), in which the primers are labeled by a fluorescent tag, and the amount of amplification product may be measured in a Taqman apparatus (Perkin-Elmer; Norwal, CT).

Targeted delivery of immunotoxins to ovarian tumor cells

The tumor marker genes of the invention can be employed as therapeutic targets for the treatment or prevention of ovarian cancer. For example, an antibody molecule that specifically binds a cell surface-localized ovarian tumor marker polypeptide can be conjugated to a radioisotope or other toxic compound. Antibody conjugates are administered to the subject such that the binding of the antibody to its cognate ovarian tumor marker polypeptide results in the targeted delivery of the therapeutic compound to ovarian tumor cells, thereby treating an ovarian cancer.

The therapeutic moiety can be a toxin, radioisotope, drug, chemical, or a protein (see, e.g., Bera et al. "Pharmacokinetics and antitumor activity of a bivalent disultide-stabilized Fv immunotoxin with improved antigen binding to erbB2" *Cancer Res.* 59:4018-4022 (1999)). For example, the antibody can be linked or conjugated to a bacterial toxin (e.g., diptheria toxin, pseudomonas exotoxin A, cholera toxin) or plant toxin (e.g., ricin toxin) for targeted delivery of the toxin to a cell expressing the ovarian tumor marker. This immunotoxin can be delivered to a cell and upon binding the cell surface-localized ovarian tumor marker polypeptide, the toxin conjugated to the ovarian tumor marker-specific antibody will be delivered to the cell.

In addition, for any ovarian tumor polypeptide for which there is a specific ligand (e.g., a ligand that binds a cell surface-localized protein), the ligand can be used in place of an antibody to target a toxic compound to an ovarian tumor cell, as described above.

Antibodies that specifically bind ovarian tumor marker polypeptides

The term "antibodies" is used herein in a broad sense and includes both polyclonal and monoclonal antibodies. In addition to intact immunoglobulin molecules, also included in the term "antibodies" are fragments or polymers of those immunoglobulin molecules and humanized versions of immunoglobulin molecules, so long as they exhibit any of the desired properties (e.g., specific binding of an ovarian tumor marker polypeptide, delivery of a toxin to an ovarian tumor cell expressing an ovarian tumor marker gene at an increased level, and/or inhibiting the activity of an ovarian tumor marker polypeptide) described herein.

Whenever possible, the antibodies of the invention may be purchased from commercial sources. The antibodies of the invention may also be generated using well-known methods. The skilled artisan will understand that either full length ovarian tumor marker polypeptides or fragments thereof may be used to generate the antibodies of the invention. A polypeptide to be used for generating an antibody of the invention may be partially or fully purified from a natural source, or may be produced using recombinant DNA techniques. For example, a cDNA encoding an ovarian tumor marker polypeptide, or a fragment thereof, can be expressed in prokaryotic cells (e.g., bacteria) or eukaryotic cells (e.g., yeast, insect, or mammalian cells), after which the recombinant protein can be purified and used to generate a monoclonal or polyclonal antibody preparation that specifically bind the ovarian tumor marker polypeptide used to generate the antibody.

In addition, one of skill in the art will know how to choose an antigenic peptide for the generation of monoclonal or polyclonal antibodies that specifically bind ovarian tumor antigen polypeptides. Antigenic peptides for use in generating the antibodies of the invention are chosen from non-helical regions of the protein that are hydrophilic. The PredictProtein Server (http://www.embl-heidelberg.de/predictprotein/subunit_def.html) or an analogous program may be used to select antigenic peptides to generate the antibodies of the invention. In one example, a peptide of about fifteen amino acids may be chosen and a peptide-antibody package may be obtained from a commercial source such as Anaspec (San Jose, CA). One of skill in the art will know that the generation of two or more different sets of monoclonal or polyclonal antibodies maximizes the likelihood of obtaining an antibody with the specificity and affinity required for its intended use (e.g., ELISA, immunohistochemistry, *in vivo* imaging, immunotoxin therapy). The antibodies are tested for their desired activity by known methods, in accordance with the purpose for which the antibodies are to be used (e.g., ELISA, immunohistochemistry, immunotherapy, etc.; for further guidance on the generation and testing of antibodies, see, e.g., Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1988). For example, the antibodies may be tested in ELISA assays, Western blots, immunohistochemical staining of formalin-fixed

ovarian cancers or frozen tissue sections. After their initial *in vitro* characterization, antibodies intended for therapeutic or *in vivo* diagnostic use are tested according to known clinical testing methods.

The term “monoclonal antibody” as used herein refers to an antibody obtained from a substantially homogeneous population of antibodies, i.e., the individual antibodies comprising the population are identical except for possible naturally occurring mutations that may be present in minor amounts. The monoclonal antibodies herein specifically include "chimeric" antibodies in which a portion of the heavy and/or light chain is identical with or homologous to corresponding sequences in antibodies derived from a particular species or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is identical with or homologous to corresponding sequences in antibodies derived from another species or belonging to another antibody class or subclass, as well as fragments of such antibodies, so long as they exhibit the desired antagonistic activity (See, U.S. Pat. No. 4,816,567 and *Morrison et al.*, Proc. Natl. Acad. Sci. USA, 81:6851-6855 (1984)).

Monoclonal antibodies of the invention may be prepared using hybridoma methods, such as those described by *Kohler and Milstein*, Nature, 256:495 (1975). In a hybridoma method, a mouse or other appropriate host animal, is typically immunized with an immunizing agent to elicit lymphocytes that produce or are capable of producing antibodies that will specifically bind to the immunizing agent. Alternatively, the lymphocytes may be immunized *in vitro*.

The monoclonal antibodies may also be made by recombinant DNA methods, such as those described in U.S. Pat. No. 4,816,567. DNA encoding the monoclonal antibodies of the invention can be readily isolated and sequenced using conventional procedures (e.g., by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of murine antibodies).

In vitro methods are also suitable for preparing monovalent antibodies. Digestion of antibodies to produce fragments thereof, particularly, Fab fragments, can be accomplished using routine techniques known in the art. For instance, digestion can be performed using papain. Examples of papain digestion are described in WO 94/29348 published Dec. 22, 1994 and U.S. Pat. No. 4,342,566. Papain digestion of

antibodies typically produces two identical antigen binding fragments, called Fab fragments, each with a single antigen binding site, and a residual Fc fragment. Pepsin treatment yields a fragment that has two antigen combining sites and is still capable of cross-linking antigen.

The antibody fragments, whether attached to other sequences or not, can also include insertions, deletions, substitutions, or other selected modifications of particular regions or specific amino acids residues, provided the activity of the fragment is not significantly altered or impaired compared to the nonmodified antibody or antibody fragment. These modifications can provide for some additional property, such as to remove/add amino acids capable of disulfide bonding, to increase its bio-longevity, to alter its secretory characteristics, etc. In any case, the antibody fragment must possess a bioactive property, such as binding activity, regulation of binding at the binding domain, etc. Functional or active regions of the antibody may be identified by mutagenesis of a specific region of the protein, followed by expression and testing of the expressed polypeptide. Such methods are readily apparent to a skilled practitioner in the art and can include site-specific mutagenesis of the nucleic acid encoding the antibody fragment. (Zoller, M.J. *Curr. Opin. Biotechnol.* 3:348-354, 1992).

The antibodies of the invention may further comprise humanized antibodies or human antibodies. Humanized forms of non-human (e.g., murine) antibodies are chimeric immunoglobulins, immunoglobulin chains or fragments thereof (such as Fv, Fab, Fab' or other antigen-binding subsequences of antibodies) which contain minimal sequence derived from non-human immunoglobulin. Humanized antibodies include human immunoglobulins (recipient antibody) in which residues from a complementary determining region (CDR) of the recipient are replaced by residues from a CDR of a non-human species (donor antibody) such as mouse, rat or rabbit having the desired specificity, affinity and capacity. In some instances, Fv framework (FR) residues of the human immunoglobulin are replaced by corresponding non-human residues. Humanized antibodies may also comprise residues which are found neither in the recipient antibody nor in the imported CDR or framework sequences. In general, the humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the CDR regions correspond to

those of a non-human immunoglobulin and all or substantially all of the FR regions are those of a human immunoglobulin consensus sequence. The humanized antibody optimally also will comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin (*Jones et al.*, Nature, 321:522-525 (1986), *Reichmann et al.*, Nature, 332:323-327 (1988), and *Presta*, Curr. Op. Struct. Biol., 2:593-596 (1992)).

Methods for humanizing non-human antibodies are well known in the art. Generally, a humanized antibody has one or more amino acid residues introduced into it from a source which is non-human. These non-human amino acid residues are often referred to as "import" residues, which are typically taken from an "import" variable domain. Humanization can be essentially performed following the method of Winter and co-workers (*Jones et al.*, Nature, 321:522-525 (1986), *Riechmann et al.*, Nature, 332:323-327 (1988), *Verhoeyen et al.*, Science, 239:1534-1536 (1988)), by substituting rodent CDRs or CDR sequences for the corresponding sequences of a human antibody. Accordingly, such "humanized" antibodies are chimeric antibodies (U.S. Pat. No. 4,816,567), wherein substantially less than an intact human variable domain has been substituted by the corresponding sequence from a non-human species. In practice, humanized antibodies are typically human antibodies in which some CDR residues and possibly some FR residues are substituted by residues from analogous sites in rodent antibodies.

Transgenic animals (e.g., mice) that are capable, upon immunization, of producing a full repertoire of human antibodies in the absence of endogenous immunoglobulin production can be employed. For example, it has been described that the homozygous deletion of the antibody heavy chain joining region (J(*H*)) gene in chimeric and germ-line mutant mice results in complete inhibition of endogenous antibody production. Transfer of the human germ-line immunoglobulin gene array in such germ-line mutant mice will result in the production of human antibodies upon antigen challenge (see, e.g., *Jakobovits et al.*, Proc. Natl. Acad. Sci. USA, 90:2551-255 (1993); *Jakobovits et al.*, Nature, 362:255-258 (1993); *Bruggermann et al.*, Year in Immuno., 7:33 (1993)). Human antibodies can also be produced in phage display libraries (*Hoogenboom et al.*, J. Mol. Biol., 227:381 (1991); *Marks et al.*, J. Mol. Biol.,

222:581 (1991)). The techniques of Cote et al. and *Boerner et al.* are also available for the preparation of human monoclonal antibodies (*Cole et al.*, Monoclonal Antibodies and Cancer Therapy, Alan R. Liss, p. 77 (19₀5) and *Boerner et al.*, J. Immunol., 147(1):86-95 (1991)].

Administration of therapeutic and diagnostic antibodies

Antibodies of the invention are preferably administered to a subject in a pharmaceutically acceptable carrier. Suitable carriers and their formulations are described in *Remington's Pharmaceutical Sciences*, 16th ed., 1980, Mack Publishing Co., edited by Oslo et al. Typically, an appropriate amount of a pharmaceutically-acceptable salt is used in the formulation to render the formulation isotonic. Examples of the pharmaceutically-acceptable carrier include saline, Ringer's solution and dextrose solution. The pH of the solution is preferably from about 5 to about 8, and more preferably from about 7 to about 7.5. Further carriers include sustained release preparations such as semipermeable matrices of solid hydrophobic polymers containing the antibody, which matrices are in the form of shaped articles, e.g., films, liposomes or microparticles. It will be apparent to those persons skilled in the art that certain carriers may be more preferable depending upon, for instance, the route of administration and concentration of antibody being administered.

The antibodies can be administered to the subject, patient, or cell by injection (e.g., intravenous, intraperitoneal, subcutaneous, intramuscular), or by other methods such as infusion that ensure its delivery to the bloodstream in an effective form. The antibodies may also be administered by intratumoral or peritumoral routes, to exert local as well as systemic therapeutic effects. Local or intravenous injection is preferred.

Effective dosages and schedules for administering the antibodies may be determined empirically, and making such determinations is within the skill in the art. Those skilled in the art will understand that the dosage of antibodies that must be administered will vary depending on, for example, the subject that will receive the antibody, the route of administration, the particular type of antibody used and other drugs being administered. Guidance in selecting appropriate doses for antibodies is found in the literature on therapeutic uses of antibodies, e.g., Handbook of Monoclonal

Antibodies, Ferrone et al., eds., Noges Publications, Park Ridge, N.J., (1985) ch. 22 and pp. 303-357; Smith et al., Antibodies in Human Diagnosis and Therapy, Haber et al., eds., Raven Press, New York (1977) pp. 365-389. A typical daily dosage of the antibody used alone might range from about 1 μg/kg to up to 100 mg/kg of body weight or more per day, depending on the factors mentioned above.

Following administration of an antibody for treating ovarian cancer, the efficacy of the therapeutic antibody can be assessed in various ways well known to the skilled practitioner. For instance, the size, number, and/or distribution of ovarian tumors in a subject receiving treatment may be monitored using standard tumor imaging techniques. A therapeutically-administered antibody that arrests tumor growth, results in tumor shrinkage, and/or prevents the development of new tumors, compared to the disease course that would occurs in the absence of antibody administration, is an efficacious antibody for treatment of ovarian cancer.

<u>Antisense and gene therapy approaches for inhibiting ovarian tumor marker gene function</u>

Because the ovarian tumor marker genes of the invention are highly expressed in ovarian tumor cells and are expressed at extremely low levels in normal ovarian cells, inhibition of ovarian tumor marker expression or polypeptide activity may be integrated into any therapeutic strategy for treating or preventing ovarian cancer.

The principle of antisense therapy is based on the hypothesis that sequence-specific suppression of gene expression (via transcription or translation) may be achieved by intracellular hybridization between genomic DNA or mRNA and a complementary antisense species. The formation of such a hybrid nucleic acid duplex interferes with transcription of the target tumor antigen-encoding genomic DNA, or processing/transport/translation and/or stability of the target tumor antigen mRNA.

Antisense nucleic acids can be delivered by a variety of approaches. For example, antisense oligonucleotides or antisense RNA can be directly administered (e.g., by intravenous injection) to a subject in a form that allows uptake into tumor cells. Alternatively, viral or plasmid vectors that encode antisense RNA (or RNA fragments) can be introduced into cells *in vivo*. Antisense effects can also be induced

by sense sequences; however, the extent of phenotypic changes are highly variable. Phenotypic changes induced by effective antisense therapy are assessed according to changes in, e.g., target mRNA levels, target protein levels, and/or target protein activity levels.

In a specific example, inhibition of ovarian tumor marker function by antisense gene therapy may be accomplished by direct administration of antisense ovarian tumor marker RNA to a subject. The antisense tumor marker RNA may be produced and isolated by any standard technique, but is most readily produced by *in vitro* transcription using an antisense tumor marker cDNA under the control of a high efficiency promoter (e.g., the T7 promoter). Administration of antisense tumor marker RNA to cells can be carried out by any of the methods for direct nucleic acid administration described below.

An alternative strategy for inhibiting ovarian tumor marker polypeptide function using gene therapy involves intracellular expression of an anti-ovarian tumor marker antibody or a portion of an anti-ovarian tumor marker antibody. For example, the gene (or gene fragment) encoding a monoclonal antibody that specifically binds to an ovarian tumor marker polypeptide and inhibits its biological activity is placed under the transcriptional control of a specific (e.g., tissue- or tumor-specific) gene regulatory sequence, within a nucleic acid expression vector. The vector is then administered to the subject such that it is taken up by ovarian tumor cells or other cells, which then secrete the anti-ovarian tumor marker antibody and thereby block biological activity of the ovarian tumor marker polypeptide. Preferably, the ovarian tumor marker polypeptide is present at the extracellular surface of ovarian tumor cells.

<u>Nucleic Acid Delivery</u>

In the methods described above which include the administration and uptake of exogenous DNA into the cells of a subject (i.e., gene transduction or transfection), the nucleic acids of the present invention can be in the form of naked DNA or the nucleic acids can be in a vector for delivering the nucleic acids to the cells for inhibition of ovarian tumor marker protein expression. The vector can be a commercially available preparation, such as an adenovirus vector (Quantum Biotechnologies, Inc. (Laval,

Quebec, Canada). Delivery of the nucleic acid or vector to cells can be via a variety of mechanisms. As one example, delivery can be via a liposome, using commercially available liposome preparations such as LIPOFECTIN, LIPOFECTAMINE (GIBCO-BRL, Inc., Gaithersburg, MD), SUPERFECT (Qiagen, Inc. Hilden, Germany) and TRANSFECTAM (Promega Biotec, Inc., Madison, WI), as well as other liposomes developed according to procedures standard in the art. In addition, the nucleic acid or vector of this invention can be delivered *in vivo* by electroporation, the technology for which is available from Genetronics, Inc. (San Diego, CA) as well as by means of a SONOPORATION machine (ImaRx Pharmaceutical Corp., Tucson, AZ).

As one example, vector delivery can be via a viral system, such as a retroviral vector system which can package a recombinant retroviral genome (see e.g., Pastan et al., *Proc. Natl. Acad. Sci. U.S.A.* 85:4486, 1988; Miller et al., *Mol. Cell. Biol.* 6:2895, 1986). The recombinant retrovirus can then be used to infect and thereby deliver to the infected cells antisense nucleic acid that inhibits expression of an ovarian tumor marker gene. The exact method of introducing the altered nucleic acid into mammalian cells is, of course, not limited to the use of retroviral vectors. Other techniques are widely available for this procedure including the use of adenoviral vectors (Mitani et al., *Hum. Gene Ther.* 5:941-948, 1994), adeno-associated viral (AAV) vectors (Goodman et al., *Blood* 84:1492-1500, 1994), lentiviral vectors (Naidini et al., *Science* 272:263-267, 1996), pseudotyped retroviral vectors (Agrawal et al., *Exper. Hematol.* 24:738-747, 1996). Physical transduction techniques can also be used, such as liposome delivery and receptor-mediated and other endocytosis mechanisms (see, for example, Schwartzenberger et al., *Blood* 87:472-478, 1996). This invention can be used in conjunction with any of these or other commonly used gene transfer methods.

As one example, if the antisense nucleic acid of this invention is delivered to the cells of a subject in an adenovirus vector, the dosage for administration of adenovirus to humans can range from about 10^7 to 10^9 plaque forming units (pfu) per injection but can be as high as 10^{12} pfu per injection (Crystal, *Hum. Gene Ther.* 8:985-1001, 1997; Alvarez and Curiel, *Hum. Gene Ther.* 8:597-613, 1997). Ideally, a subject will receive a single injection. If additional injections are necessary, they can be repeated at six

month intervals for an indefinite period and/or until the efficacy of the treatment has been established.

Parenteral administration of the nucleic acid or vector of the present invention, if used, is generally characterized by injection. Injectables can be prepared in conventional forms, either as liquid solutions or suspensions, solid forms suitable for solution of suspension in liquid prior to injection, or as emulsions. A more recently revised approach for parenteral administration involves use of a slow release or sustained release system such that a constant dosage is maintained. See, e.g., U.S. Patent No. 3,610,795, which is incorporated by reference herein. For additional discussion of suitable formulations and various routes of administration of therapeutic compounds, see, e.g., *Remington: The Science and Practice of Pharmacy* (19th ed.) ed. A.R. Gennaro, Mack Publishing Company, Easton, PA 1995.

Example I: Identification of ovarian tumor marker genes using SAGE

Serial Analysis of Gene Expression is a method that enables the global analysis of gene expression from a tissue of interest (Velculescu et al., *Science* 270:484-487, 1995; Zhang et al., *Science* 276:1268-72, 1997). The advantages of SAGE over cDNA arrays, another method for the global analysis of gene expression, include: 1) the possibility of identifying novel genes, 2) determination of absolute levels of gene expression, which is difficult in hybridization-based techniques, and, 3) examination of gene expression as a whole instead of as a subset of genes.

Construction and screening of SAGE libraries

The SAGE technique has been described in detail (Velculescu et al., *Science* 270:484-487, 1995). The SAGE libraries disclosed herein were made as described by Velculescu, *supra*. First, total RNA was purified from the cells. Poly A+ RNA was then isolated and reverse transcription was performed using a biotinylated poly dT primer for first strand synthesis. The cDNA mixture was cut with *Nla*III and the biotinylated 3' fragments were collected using streptavidin beads. The beads were divided into two aliquots (A and B) and linkers containing PCR primer sites and a site for class II restriction enzyme *Bsm*FI were ligated to the DNA fragments attached to the

beads from samples A and B. The mixture was treated with the restriction enzyme *BsmFI*, which recognizes the site in the linker but cuts 14 bp downstream. The resulting fragments contained the linker and 10 bp of "cDNA sequence" that is referred to as "tag". The tags from samples A and B were ligated together to form ditags, which were then amplified by PCR. Any repeated ditag (tags containing the same two individual tags) are an indication of PCR bias and were eliminated by the SAGE software (Velculescu et al., *Science* 270:484-487, 1995; Zhang et al., *Science* 276:1268-72, 1997). The tags were concatemerized and cloned into a sequencing vector. Sequencing revealed the identity and frequency of the different tags. As described above, the 10 bp tag is sufficient to identify cDNA and the frequency of a particular tag represents the frequency of a particular message in the population. The SAGE software developed in the laboratories of Bert Vogelstein and Kenneth Kinzler at Johns Hopkins extracts the tags from the raw sequencing data, matches the tags to the corresponding genes (present in Genbank) and makes frequency comparisons between the tags from an individual library or other libraries.

Verification of ovarian tumor marker genes identified by SAGE

The most promising candidates are selected and verified by any expression analysis method, e.g., Northern analysis or reverse transcription-polymerase chain reaction (RT-PCR). For Northern analysis, radioactive probes are generated from expressed sequence tags (ESTs) corresponding to the candidate genes and are used to hybridize to membranes containing total RNA from various ovarian cancers and controls. The candidates may also be verified by real-time PCR using the Taqman method (Heid and Stevens, *Genome Res.* 6:986-94, 1996). Amplification primers and fluorescent probes are synthesized according to instructions from the manufacturer (Perkin-Elmer; Norwalk, CT). Quantitative PCR is performed using a PE 5700 apparatus or an analogous instrument.

Sources of RNA for SAGE library construction

Eleven SAGE libraries were constructed, as shown in Table 1. The human ovarian surface epithelial cell (HOSE) library was constructed using RNA from HOSE

cells that were obtained by gently scraping the ovarian surface from a hysterectomy patient followed by short-term *in vitro* culture (three passages) of the cells. Three of the ovarian tumor libraries (designated OVT6, OVT7, and OVT8) were constructed using RNA from one of three primary high grade serous adenocarcinomas. Libraries from individual ovarian tumor cell lines were generated using RNA from OV1063 (derived from an ovarian papillary adenocarcinoma; obtained from the American Type Culture Collection (ATCC; Manassas, VA; CRL-2183)); ES-2 (derived from a clear cell adenocarcinoma; from the ATCC; CRL-1978); A2780 (derived from an ovarian cancer; obtained from Dr. Vilhelm Bohr, Baltimore, MD); OVCA432 (derived from an ovarian serous cystadenocarcinoma; Bast et al., *J. Clin. Invest.* 68:1331-1337, 1981); ML10 (derived from an ovarian cystadenoma; Luo et al. *Gyn. Oncol.*, 67:277-284, 1997); or IOSE29 (simian virus 40-immortalized OSE cells; Auersperg et al., *Proc. Natl. Acad. Sci. USA* 96:6249-6254, 1999).

The pooled library was generated using RNA from a pool of 10 cell lines: A2780; BG-1 (poorly differentiated ovarian cancer; obtained from Dr. Carl Barrett, Durham, NC); ES-2; OVCA432; MDAH 2774 (endometrioid adenocarcinoma; obtained from the ATCC); and five cell lines obtained from Dr. Michael Birrer (Rockville, MD): AD10 (an adriamycin-resistant derivative of A2780); A222 (ovarian carcinoma); UCI101 (papillary ovarian adenocarcinoma); UCI107 (papillary ovarian adenocarcinoma); and A224 (ovarian carcinoma).

TABLE 1

Library	Seq	Tags (raw)	Tags	Genes	At least 2
HOSE	2,290	49,394	47,881	16,034	4,532
OVT6	2,104	43,891	41,620	18,476	4,799
OVT7	2,089	57,725	53,898	19,523	5,669
OVT8	2,076	36,813	32,494	16,363	3,815
OV1063	2,146	41,131	37,862	15,231	4,746
ES-2	1,775	36,430	35,352	14,739	3,952
A2780**	475	9,269	8,246	5,179	1,021
OVCA432	384	3,011	2,824	1,940	310
Pool	2,201	10,952	10,554	5,956	1,627
ML10	1,935	61,083	55,700	18,727	6,637
IOSE29	*	*	*	*	*
TOTAL	17,475	349,699	326,431	75,056	25,071

* To be sequenced
**Incomplete

Results of SAGE

Eleven ovarian SAGE libraries were constructed, ten of which have been sequenced to date. The overall data are summarized in Table 1 above. For each SAGE library, Table 1 shows the number of SAGE library clones sequenced, the number of raw tags sequenced, the number of tags obtained after correction for PCR bias, the total number of genes that are represented by the corrected pool of tags, and the number of genes that were represented at least twice in the corrected pool of tags. For most libraries, 35,000-61,000 tags were obtained, yielding anywhere from 14,000-20,000 genes. In total, 75,056 genes were identified.

In order to identify genes that are up-regulated in ovarian tumors and that may serve as diagnostic markers and therapeutic targets, we compared gene expression between the normal ovarian cells (HOSE) and the cancer cells (OVT6, OVT7, OVT8, OV1063, ES2, A2780, Pool). OVCA432 was not included in this analysis because of the poor number of tags obtained from this library. We looked for genes for which expression was absent or low (frequency smaller or equal to 2 tags per 100,000) in HOSE and at least 7- to 10-fold up-regulated in the majority of the tumor libraries, and detected a number of genes matching these criteria. Table 2 shows the libraries that were screened, the SAGE tags that were identified in the library screens, along with their corresponding genes and Genbank accession numbers, and the relative expression of each gene in each library. Any one of these ovarian tumor marker genes may be used in the diagnostic and/or therapeutic methods of the invention.

TABLE 2

SEQ. ID NO. (Tag)	Tag	OVT8	OVT7	OVT6	A2780	OV1063	ES2	Pool	HOSE	Gene Product	Genbank
83	TCAGACGCAG	52	149	91	97	49	214	82	2	Prothymosin, alpha	M14483
84	TTATGGGATC	57	80	57	140	83	126	274	2	G protein, beta polypeptide 2-like 1	M24194
85	CCCGCCCCCG	136	166	52	22	7	0	146	2	Lutheran blood group (B-CAM)	NM_005581
86	GAGGAAGAAG	14	38	57	76	53	80	100	2	Tumor rejection antigen-1 (gp96) 1	NM_003299
87	GAAGCTTTGC	27	43	43	22	27	66	73	2	HSP90	AA071048
88	TACCAGTGTA	30	16	14	140	22	30	100	2	HSP60	M22382
89	TCTTCTCCCT	8	42	32	22	27	25	46	2	Hepatoma-Derived Growth Factor (HDGF)	D16431
90	TTGGCTTTTC	14	12	71	32	10	22	18	0	DKFZp5860031	AL117237
91	GGAAGGGAGG	30	14	16	11	12	44	55	2	CD63 antigen (melanoma 1 antigen)	AA041408
92	AAGCCAGCCC	19	17	36	22	17	27	18	2	Protein kinase C substrate 80K-H	J03075
93	TTTCAGATTG	16	26	25	32	22	19	18	0	Polymerase II cofactor 4 (PC4)	X79805
94	GCATAGGCTG	11	24	25	22	12	27	9	2	Tu translation elong. factor (mitochondrial)	L38995
95	TTTGTTAATT	30	16	16	43	17	19	18	2	hNRP H1	L22009
96	GAGACTCCTG	11	23	23	22	12	3	64	2	Solute carrier family 2	AF070544
97	CCTGTAATTC	19	10	27	32	15	8	27	2	KIAA0591 protein	AB011163
98	GTGGTGCGTG	16	10	21	11	15	19	27	2	X-ray repair protein	AF035587
99	TTGGACCTGG	11	19	9	11	27	16	18	2	ATP synthase (delta subunit)	AA524164
100	CTTAAGGATT	11	12	18	11	15	27	9	0	DKFZP564M2423 protein	BC003049
101	GTCTGTGAGA	8	17	9	22	12	22	18	0	Growth factor-regul. tyr kinase substrate	D84064
102	GAAACTGAAC	16	10	14	32	12	3	9	2	eIF-2-associated p67	U29607

Example II: Identification of additional ovarian tumor marker genes using SAGE

Serial Analysis of Gene Expression (SAGE) was used to generate global gene expression profiles from various ovarian cell lines and tissues, including primary cancers, ovarian surface epithelial (OSE) cells and cystadenoma cells. The profiles were used to compare overall patterns of gene expression and identify differentially expressed genes. We have sequenced a total of 385,000 tags, yielding over 56,000 genes expressed in ten different libraries derived from ovarian tissues.

In general, ovarian cancer cell lines showed relatively high levels of similarity to libraries from other cancer cell lines, regardless of the tissue of origin (ovarian or colon), indicating that these lines had lost many of their tissue specific expression patterns. In contrast, immortalized OSE (IOSE) and ovarian cystadenoma cells showed much higher similarity to primary ovarian carcinomas as compared to primary colon carcinomas. Primary tissue specimens therefore appeared to be a better model for gene expression analyses. Using the expression profiles described above and stringent selection criteria, we have identified a number of genes highly differentially expressed between non-transformed ovarian epithelia and ovarian carcinomas. Some of the genes identified are already known to be overexpressed in ovarian cancer but several represent novel candidates. Many of the genes up-regulated in ovarian cancer represent surface or secreted proteins such as Claudin-3 and -4, HE4, Mucin-1, Ep-CAM and Mesothelin. The genes encoding apolipoprotein E (ApoE) and apolipoprotein J (ApoJ), two proteins involved in lipid homeostasis are among the genes highly up-regulated in ovarian cancer. Selected SAGE results were further validated through immunohistochemical analysis of ApoJ, Claudin-3, Claudin-4 and Ep-CAM in archival material. These experiments provided additional evidence of the relevance of our findings *in vivo*.

A) METHODS

Cell Culture and Tissue Samples

Ovarian cancer cell lines OV1063, ES2, and MDAH 2774 were obtained from the American Type Culture Collection (Manassas, VA). Cell lines A222, AD10, UCI101 and UCI107 were obtained from Dr. Michael Birrer (Rockville, MD). Cell line A2780 was obtained from Dr. Vilhelm Bohr (Baltimore, MD). The SV40-

immortalized cell lines IOSE29 (Auersperg, N., et al. *Proc. Natl Acad. Sci. USA*, 96:6249-6254, 1999) and ML10 (Luo, M. P., et al. *Gynecol. Oncol.* 67:277-284, 1997) were kindly provided by Dr. Nelly Auersperg (British Columbia, Canada) and Dr. Louis Dubeau (Los Angeles, CA), respectively. Except for IOSE29, ML-10 and HOSE-4, all cell lines were cultured in McCoy's 5A growth medium (Life Technologies, Inc, Gaithersburg, MD) supplemented with 10% fetal bovine serum (FBS) and antibiotics (100 U/ml of Penicillin and 100 ug/ml Streptomycin). IOSE29 was cultivated in Medium 199 (Life Technologies, Inc, Gaithersburg, MD) supplemented with 5% newborn calf serum (NCS). ML10 was cultivated in MEM (Life Technologies, Inc, Gaithersburg, MD) supplemented with 10% FBS and antibiotics as above.

Three high-grade serous ovarian cancer specimens, OVT6, OVT7, and OVT8, composed of at least 80% tumor cells as determined by histopathology, were chosen for SAGE. The ovarian tumor samples were frozen immediately after surgical resection and were obtained form the Johns Hopkins gynecological tumor bank in accordance with institutional guidelines on the use of human tissue. Normal human ovarian surface epithelial (HOSE-4) cells were cultured from the right ovary of a patient undergoing hysterectomy and bilateral salpingo-oophorectomy for benign disease. The OSE cells were obtained by gently scraping the surface of the ovary with a cytobrush and grown for 2 passages in RPMI 1640 medium supplemented with 10% FBS and 10 ug/ml insulin-like growth factor (IGF).

Serial Analysis of Gene Expression (SAGE)

Total RNA was obtained from guanidinium isothiocyanate cell lysates by centrifugation on CsCl. Polyadenylated mRNA was purified from total RNA using the Messagemaker kit (Life Technologies, Gaithersburg, MD) and the cDNA generated using the cDNA Synthesis System (Life Technologies, Gaithersburg, MD). For the "Pool" library, 100 ug of total RNA from each of 10 ovarian cancer cell lines (A222, A2780, AD10, BG-1, ES-2, MDAH 2774, OVCA432, OV1063, UCI101 and UCI107) were combined and mRNA purified. SAGE was performed essentially as described (Velculescu, V. E., et al. *Science* 270:484-487, 1995) for all the libraries except HOSE. To create the HOSE library, MicroSAGE, a modified SAGE technique developed for limited sample sizes (Datson, N. A., et al. *Nucleic Acids Res.* 27:1300-1307, 1999),

was used. Approximately $1X10^6$ OSE cells in short-term culture were lysed and the mRNA purified directly using Oligo $(dT)_{25}$ Dynabeads (Dynal, Norway). As part of the Cancer Genome Anatomy Project (CGAP) SAGE consortium, the SAGE libraries were arrayed at the Lawrence Livermore National Laboratories and sequenced at the Washington University Human Genome Center or NISC (NIH, Bethesda, MD). The data has been posted on the CGAP website (http://www.ncbi.nlm.nih.gov/SAGE/) as part of the SAGEmap database (Lal, A., et al. *Cancer Res.* 59:5403-5407, 1999.).

Sequence data from each library were analyzed by the SAGE software (Velculescu, V. E., et al. *Science* 270:484-487, 1995.) to quantify tags and identify their corresponding transcripts. The data for the colon libraries NC1, NC2, Tu98, Tu102, HCT116 and SW837 were obtained from the SAGEmap database and analyzed in the same way. Because the different libraries contained various numbers of total tags, normalization (to 100,000 tags) was performed to allow meaningful comparisons. The 10,000 most highly expressed genes in each of the 16 SAGE libraries of interest were formatted in a Microsoft Excel spreadsheet and Pearson correlation coefficients were calculated for each pair-wise comparison using normalized tag values for each library. The value for the Pearson correlation coefficient (r) represents the degree of similarity (the strength of the relationship) between two libraries and is calculated using the following equation:

$$\boxed{r = \frac{n(\Sigma xy) - (\Sigma x)(\Sigma y)}{\sqrt{[n\Sigma x^2 - (\Sigma x)^2][n\Sigma y^2 - (\Sigma y)^2}}}$$

where, x_i =number of tags per 100,000 for tag i in the first library and y_i=number of tags per 100,000 for tag i in the second library. For our purposes n equals 10,000 since 10,000 tags are compared. A dendrogram representing the hierarchical relationships between samples was then generated using hierarchical cluster analysis as described (Eisen, M. B., et al. *Proc. Natl Acad. Sci. USA* 95:14863-14868, 1998). In addition, the identification of differentially expressed genes was also done using this subset of the SAGE data.

Immunohistochemistry

Deparafinized 5-um sections of formalin-fixed ovarian cancer specimens were submitted to heat-induced antigen retrieval and processed using the LSAB2 system

(DAKO, Carpinteria, CA) with 3,3'-diaminobenzidine as the chromatogen and a hematoxylin counterstain. Monoclonal antibody against ApoJ/Clusterin (Clone CLI-9) was obtained from Alexis Corporation (San Diego, CA) and used at a 1:500 Dilution. Monoclonal antibody against Ep-CAM (Clone 323/A3) from NeoMarkers (Fremont, CA) was used at a 1:500 dilution. Polyclonal antibodies against Claudin-3 and -4 were a generous gift from Drs. M. Furuse and S. Tsukita (Kyoto, Japan) and were used at a dilution of 1:1000.

B) RESULTS

Ovarian SAGE library construction and analysis

Gene expression alterations that arise during malignant transformation can be identified a number of ways. We chose the unbiased, comprehensive method SAGE to create global gene expression profiles from ten different ovarian sources. The expression patterns are generated by sequencing thousands of short sequence tags that contain sufficient information to uniquely identify the corresponding transcripts (Velculescu, V. E., et al. *Science* 270:484-487, 1995). Ten different SAGE libraries were constructed and sequenced for this study (Table 3). Our libraries included two derived from OSE cells (IOSE29 and HOSE-4), one derived from immortalized cystadenoma cells (ML-10), three primary tumors (OVT-6, -7, -8) and four libraries derived from ovarian cancer cell lines (OV-1063, ES-2, A2780 and a pool of cell lines). Almost 20,000 sequencing reactions were performed yielding a total of 384,497 tags, of which, 82,533 were unique. Accounting for a SAGE tag error rate of 6.8% (due to sequencing errors; see Zhang, L., et al., *Science* 276:1268-1272, 1997), we estimate that we have identified a total of 56,387 genes expressed in ovarian tissues. Except for the A2780 cell line and the pooled lines (POOL) samples, a minimum of 12,000 genes were obtained from every library. Typically, for each library, 10% of the genes were expressed at levels of at least 0.01% and, collectively, these genes accounted for more than 50% of all the tags sequenced. Among the tags that appeared more than once, up to 95% matched to known sequences in the current Genbank nr database. For example, of the 6637 tags that appeared more than once in ML10, only 311 had no matches in the current database, excluding the EST databases.

Table 3 *Summary of SAGE library analyses*

Library [a]	Sequence	Tags [b]	Unique tags [c]	Genes [d]	≥ 2 tags [e]
HOSE	2,290	47,881	16,034	12,778	4,532
IOSE	1,912	47,549	18,004	14,771	5,681
ML10	1,935	55,700	18,727	14,939	6,637
OVT6	2,104	41,620	18,476	15,646	4,799
OVT7	2,089	53,898	19,523	15,858	5,669
OVT8	2,076	32,494	16,363	14,153	3,815
OV1063	2,146	37,862	15,231	12,656	4,746
A2780	1,332	21,587	10,717	9,249	2,761
ES2	1,775	35,352	14,739	12,335	3,952
POOL	2,201	10,554	5,956	5,238	1,627
TOTAL	19,860	384,497	82,533	56,387	28,219

[a] The libraries are: HOSE, human ovarian surface epithelium from short term culture; IOSE, SV40-immortalized ovarian surface epithelium; ML10, SV40-immortalized benign cystadenoma; OVT6, OVT7, and OVT8, primary ovarian serous adenocarcinomas; OV1063, A2780, and ES2, ovarian cancer cell lines; POOL, a pool of ten ovarian cancer cell lines.
[b] Tag numbers after elimination of linker-based tags and duplicate ditags.
[c] The number of unique tags identified in each library.
[d] The number of genes identified after correction for sequencing errors.
[e] The number of genes represented at least twice.

Comparisons of global gene expression between ovarian tissue samples

Although progression to malignancy requires a number of gene expression changes, the transcript levels from the vast majority of genes remain unaltered (Zhang, L., et al., *Science* 276:1268-1272, 1997; and Alon, U., et al., *Proc. Natl Acad. Sci. USA* 96:6745-6750, 1999). Similarities between the global expression profiles of two given samples can be readily visualized using scatterplots and quantitated through the calculation of Pearson correlation coefficients. Scatterplots of global gene expression analysis in IOSE (ovarian) vs. ML10 (ovarian), OVT6 (ovarian), or Tu98 (colon) cells were generated using the Spotfire Pro 4.0 software (Cambridge, MA) and the Pearson correlation coefficients for each pair-wise comparison of the 16 ovarian and colon SAGE libraries were calculated.

As expected, the immortalized IOSE29 and ovarian cystadenoma strain ML10 are much more similar to ovarian tumors than to colon tumors (average correlation coefficients of 0.70 vs. 0.51, respectively). In addition, IOSE29 and ML10 are very similar to each other, with a correlation coefficient of 0.82. The primary culture of OSE cells (HOSE-4) exhibited higher similarities to the ovarian tumors than to the colon tumors, although the similarity levels were much lower than those observed for IOSE29. Interestingly, HOSE-4 and IOSE29 appear to be much more distantly related than expected considering the fact that they were both derived from "normal" OSE cells. The differences in gene expression between these cells may be due to a number of factors. The age of the patient, the pathological state of the ovaries, the presence of non-epithelial cells in the culture and the fact that IOSE29 is SV40-immortalized may all contribute to the gene expression differences observed. However, it is unlikely that the main differences are due to SV40-immortalization since IOSE29 is much more similar to normal colon (a non SV40-immortalized epithelium) than HOSE-4. It is, of course, possible that the lower degree of similarity between HOSE-4 and the ovarian tumors compared to IOSE29 and ML-10 reflects the fact that HOSE-4 represents a better approximation of the normal *in vivo* OSE cell.

Three dendrograms were created from hierarchical cluster analysis of all colon and ovarian SAGE libraries, ovarian samples only, and non-malignant ovarian and colon epithelia as well as ovarian and colon primary tumors, using Cluster software (Eisen, M. B., et al. *Proc. Natl Acad. Sci. USA* 95:14863-14868, 1998). When all the

samples were included in the hierarchical clustering analysis, the primary colon tumors clustered with the normal colon epithelium, but colon cell lines clustered with the ovarian specimens. Clearly, the tissue clustering that was readily apparent when comparing primary tissues or immortalized lines was lost when including carcinoma cell lines. For example, A2780, a widely used ovarian cancer cell line was just as similar to colon cancer cell lines as it was to ovarian cancer cell lines. This observation supports the idea that in the process of establishment, cell lines may lose many of the gene expression characteristics of their tissue of origin, although tissue specific expression is clearly not completely lost in cancer cell lines (Ross, D. T., et al. *Nat. Genet.* 24:227-235, 2000).

It is widely believed that epithelial ovarian cancer and benign ovarian cysts, while not necessarily part of a progression sequence toward malignancy, are both derived from the ovarian surface epithelium (Scully, R. E. *J. Cell Biochem.* 23, Suppl.:208-218, 1995). OSE cells themselves are mesodermal in origin and are believed to undergo metaplasia before progressing to neoplasia (Scully, R. E. *J. Cell Biochem.* 23 Suppl.:208-218, 1995; and Maines-Bandiera, S. L. and Auersperg, N. *Int. J. Gynecol. Pathol.* 16:250-255, 1997). On the other hand, it has also been argued that ovarian cancers are not derived from OSE but rather from the secondary Mullerian system, structures lined by Mullerian epithelium but located outside the uterus, cervix and fallopian tubes (Schink, J. C. *Semin. Oncol.* 26 Suppl. 1: 2-7, 1999). This hypothesis would explain some of the shortcomings of the OSE model, such as the requirement for metaplasia and the lack of well-defined precursors in the ovary. While not wishing to be bound by theory, our results are consistent with the widely accepted dogma of the OSE origin of ovarian cancer. Indeed, IOSE29 showed high degrees of similarity to the ovarian tumors and both IOSE29 and HOSE were much more closely related to ovarian than colon primary cancers.

E-cadherin expression has been proposed to be a major determinant in the formation of metaplastic OSE (Auersperg, N., et al. *Proc. Natl Acad. Sci. USA*, 96:6249-6254, 1999; and Maines-Bandiera, S. L. and Auersperg, N. *Int. J. Gynecol. Pathol.* 16:250-255, 1997). Consistent with this hypothesis, E-cadherin was absent in IOSE29, HOSE and ML10 but was expressed in all three ovarian tumors (Table 4). Other cadherins are also shown for comparison. Interestingly, VE-cadherin is absent in

most libraries except in two of the pre-neoplastic ovarian samples, again suggesting metaplasia. As expected, LI-Cadherin was expressed exclusively in the colon-derived libraries. Interestingly, vimentin, a mesenchymal marker, was present in essentially all the ovarian libraries but very low in the colon specimens. Although the specificity of vimentin as a mesenchymal marker has been questioned, this suggests that OSE may retain some of their mesenchymal characteristics, even after turning on the expression of E-cadherin.

The cytokeratins (CKs) and carcinoembryonic antigen (CEA) have been used to differentiate between colon cancer and ovarian cancer (Lagendijk, J. H., et al. *Hum. Pathol.* 29:491-497, 1998; and Berezowski, K., et al. *Mod. Pathol.* 9:426-429, 1996). Typically, colon cancer expresses CK20 and CEA while ovarian cancer expresses CK7. The expression patterns in our libraries were consistent with previously reported observations: CK20 and CEA were found in normal colon and colon tumors but absent from all of our ovarian samples (Table 4). Conversely, CK7 was expressed in all three primary ovarian tumors and, while not absent, was much lower in the colon samples. Examination of the differential expression patterns of a variety of established ovarian cancer markers thus provided validation of the SAGE database and cluster analysis.

Differential gene expression

The ultimate goal of comparing SAGE libraries is to identify differentially expressed genes. Criteria for differential expression can be determined for each comparison and transcripts within the determined range selected for study. We found a large number of genes that were up-regulated in only one or two of the three tumors on which SAGE was performed. For example, a total of 444 genes were up-regulated more than 10-fold in at least one of the three ovarian primary cancers compared to IOSE29. However, only 45 genes were overexpressed more than 10-fold in all three ovarian tumors analyzed compared to IOSE29.

Our analysis of three different primary ovarian cancers allowed us to reduce the number of candidates by looking for consistency between samples. In order to identify genes that are very likely to be frequently up-regulated during ovarian tumorigenesis we set the following conservative criteria for our analysis. First, the fold induction was calculated by adding the number of normalized tags from the three primary tumors and

dividing this number by the total normalized tags in the three non-malignant specimens. Cell lines were not included here for reasons described above. In addition, although HOSE-4 appeared more distantly related to the other non-transformed specimens, we believe that the inclusion of HOSE-4, while possibly eliminating real candidates makes our analysis more conservative and more likely to identify truly overexpressed genes in ovarian cancer. Second, all three primary tumors were required to consistently show elevated levels (>12 tags/100,000) of the gene in question. This eliminated genes that may be very highly overexpressed in one tumor but not in others. Finally, the candidate genes were required to be expressed in at least one ovarian cell line at a level greater than 3 tags/100,000. This last criterion was used to reduce the possibility of identifying genes because of their high level of expression in inflammatory cells or in the stroma of the primary tumors. Using these criteria, the genes that exhibited more than 10-fold overexpression were identified and are shown in Table 4.

Two members of the Claudin family of tight junction proteins, Claudin-3 and -4 were found among the top six differentially expressed genes and likely represent transmembrane receptors. In addition, Apolipoprotein J (ApoJ) and Apolipoprotein E (ApoE) were both overexpressed in ovarian cancer.

Of the 27 overexpressed genes shown in Table 4, ten were relatively specific for the ovary (HLA-DR, two different ESTs, GA733-1, ceruloplasmin, glutathione peroxidase-3, the secretory leukocyte protease inhibitor, ApoJ, ApoE and mesothelin) while the others were also expressed in colon tissues. In any event, it is significant that MUC1, HE4, Ep-CAM and mesothelin, four genes already known to be up-regulated in epithelial ovarian cancer, were identified in this study. This fact validates our approach as well as our set of criteria used to determine the genes differentially expressed.

Similarly, stringent criteria were used to identify genes down-regulated in ovarian tumors compared to IOSE29, HOSE-4 and ML10. Again, the fold difference was calculated by adding tag frequency for all three "normal" specimens and dividing by the total number of tags in the three ovarian tumors. A candidate was required to be expressed at a level of 12 tags/100,000 or greater in all three normal samples. The genes found elevated more than ten-fold in normal tissue compared to tumors are shown in Table 4.

Table 4. A subset of genes differentially expressed in ovarian tumors compared to non-malignant ovarian samples

SEQ ID NO. (TAG)	TAG	GENE	EXPRESSION[c]					FUNCTION
			Fold	OSE ML10	Ovarian Tumors	Colon Epithelium	Colon Tumors	
		up-regulated[a]						
103	GGGCATCTCT	HLA-DR α chain	289	-	++	-	-	Major histocompatibility complex, class II/ antigen presentation
104	TTTGGGCCTA	Cysteine-rich protein 1	123	-	++	+	-	LIM/double zinc finger
105	ATCGTGGCGG	Claudin 4	109	-	+	++	+	Tight junction barrier function
106	TATTATGGTA	ESTs (HOST-2)	101	-	+	-	-	Unknown
107	GCCTACCCGA	Surface marker 1/ GA733-1/ TROP2	93	-	+	-	-	Tumor Ag/ Ca^{2+} signal transducer
108	CTCGCGCTGG	Claudin 3	83	-	+	++	+	Tight junction barrier function
109	TTGCTTGCCA	Ceruloplasmin (ferroxidase)	79	-	+	-	-	Secreted metalloprotein/ antioxidant
110	CCTGCTTGTC	HE4	72	-	++	+	-	Secreted protease inhibitor
111	AGGGAGGGGC	Glutathione peroxidase 3 (plasma)	69	-	+	-	-	Secreted selenoprotein/ peroxidase
112	TGTGGGAAAT	Secretory leukocyte protease inhibitor	60	-	++	-	-	Secreted serine protease inhibitor
113	CCTGATCTGC	ESTs (HOST-1)	56	-	+	-	-	Unknown
114	ACCATTGGAT	Interferon-induced transmembrane protein 1	49	-	++	-	+	Receptor for interferon signaling
115	AGTTTGTTAG	Ep-CAM/ EGP2/ TROP1/ GA733-2	48	-	+	++	+	Tumor Ag/ Ca^{2+}-independent CAM/ proliferation
116	CCTGGGAAGT	Mucin 1	43	-	++	+	+	Tumor Ag/ Type-I membrane glycoprotein
117	CAACTAATTC	Apolipoprotein J/ clusterin	39	-	++	-	-	Secreted chaperone/ cytoprotection
118	GCCTGCAGTC	Serine protease inhibitor, Kunitz type, 2	34	-	++	++	+	Transmembrane/ protease inhibitor
119	CGACCCCACG	Apolipoprotein E	34	-	++	-	-	Lipoprotein particle binding, internalization and catabolism
120	TTCTGTGCTG	Complement component 1, r subcomponent	24	-	+	-	-	Serine protease of complement system/ autoimmune diseases
121	CGCCGACGAT	G1P3/ IFI-6-16	24	-	++	+	+	Interferon primary response/ α IFN-inducible
122	CCCGCCCCCG	Lutheran blood group protein/ BCAM	17	-	++	-	-	Possible cell surface receptor/ immunoglobulin superfamily
123	GATCAGGCCA	Collagen Type III, alpha-1	16	-	++	-	+	Unknown
124	GTGGAAGACG	Mal (T cell differentiation protein)	16	-	+	-	-	Trans-Golgi membrane protein (epithelial cells)/ T-cell differentiation
124	GATGAGGAGA	ESTs (Collagen Type I, alpha-2	13	+	++	-	+	Unknown
126	TTCCCTTCTT	HLA-DPB1	13	-	+	-	-	Major histocompatibility complex, class II/ antigen presentation
127	CCCCCTGCAG	Mesothelin	12	-	++	-	-	GPI-anchored/ mesothelioma and ovarian cancer antigen/ cell adhesion
128	TGCTGCCTGT	Bone marrow stroma antigen 2/ BST-2	12	-	++	-	+	Type II transmembrane protein/ pre-B-cell growth
129	TGCAGCACGA	HLA-Cw	10	-	++	++	+	Major histocompatibility complex, class I/ antigen presentation
		down-regulated[b]						
130	GGTTATTTTG	Unknown	99	+	-	-	-	Unknown
131	TGTCATCACA	Lysyl oxidase-like 2	73	+	-	-	-	Secreted/ collagen and elastin crosslinker
132	AAAATAAACA	Chloride intracellular channel 4 like	29	+	-	-	-	Ion transport
133	TAAAAATGTT	Plasminogen activator inhibitor, type 1	26	++	-	-	-	Serine protease inhibitor family/ tPA inhibitor
134	GAGCTTTTGA	EST	14	+	-	-	-	Unknown
135	GGCTGATGTG	Glycine t-RNA synthetase	13	+	-	-	-	Protein synthesis
136	CGACGAGGAG	Epithelial membrane protein-3	13	+	-	-	-	Proliferation, differentiation, and apoptosis
137	GCCCCCAATA	Galectin-1	10	++	+	-	-	β-galactoside binding lectin/ ECM interaction and proliferation
138	GCAACTTGGA	Vinexin β	10	+	-	-	-	Cell-adhesion and cytoarchitecture

[a] Candidates up-regulated at least 30-fold in tumors
[b] Candidates down-regulated at least 10-fold in tumors
[c] Expression is defined as: -, 0-9 tags/100,000; +, 10-49 tags/100,000; ++, > 49 tags/100,000

In order to validate the candidates identified by SAGE, we performed immunohistochemical analysis of thirteen cases of serous cancer of the ovary using antibodies against four of the genes identified as up-regulated in ovarian cancer (Table 5). This was particularly important since the SAGE analysis was initially performed from primary ovarian cancers, which contain a mixture of cell types. Ep-CAM exhibited diffuse, strong staining of tumor cell membranes in all thirteen tumors, without blood cell or stromal staining. Importantly, only one of six samples of the ovarian surface epithelium present in the cases showed weak focal staining, and the rest were negative. The strong immunoreactivity of all thirteen ovarian tumors confirms the validity of our approach to identify genes highly and consistently up-regulated in ovarian cancer. Similarly, ApoJ was found to be expressed in ovarian cancer cells and absent from the surface epithelium. While some expression was detected in non-tumor stroma and inflammatory cells, most of the immuno-reactivity was in tumor cells, and a majority (nine out of thirteen) of the cases showed staining. This observation represents the first report of ApoJ expression in ovarian cancer and provides a novel target for diagnosis or therapy. Claudin-3 and -4 also exhibited staining limited to the tumor component of the specimens. Most tumor cells showed strong membrane staining with weak cytoplasmic reactivity. Some tumors specimens showed decreased membrane staining with strong cytoplasmic reactivity. The normal surface epithelial component (or mesothelial cells) examined did not stain or only stained weakly with the Claudin-4 antibody, while the determination of Claudin-3 levels in normal epithelium was complicated by a low background reactivity with this antibody.

<u>Incorporation by Reference</u>

Throughout this application, various publications, patents, and/or patent applications are referenced in order to more fully describe the state of the art to which this invention pertains. The disclosures of these publications, patents, and/or patent applications are herein incorporated by reference in their entireties to the same extent as if each independent publication, patent, and/or patent application was specifically and individually indicated to be incorporated by reference.

Other Embodiments

It will be apparent to those skilled in the art that various modifications and variations can be made in the present invention without departing from the scope or spirit of the invention. Other embodiments of the invention will be apparent to those skilled in the art from consideration of the specification and practice of the invention disclosed herein. It is intended that the specification and examples be considered as exemplary only, with a true scope and spirit of the invention being indicated by the following claims.

What is claimed is:

1. A method of detecting an ovarian tumor in a subject, said method comprising measuring the expression level of an ovarian tumor marker gene in said subject, wherein an increase in said expression level of said ovarian tumor marker gene in said subject, relative to the expression level of said ovarian tumor marker gene in a reference subject not having an ovarian tumor, detects an ovarian tumor in said subject.

2. A method of identifying a subject at increased risk for developing ovarian cancer, said method comprising measuring the expression level of an ovarian tumor marker gene in said subject, wherein an increase in said expression level of said ovarian tumor marker gene in said subject, relative to the expression level of said ovarian tumor marker gene in a reference subject not at increased risk for developing ovarian cancer, identifies an individual at increased risk for developing ovarian cancer.

3. A method of determining the effectiveness of an ovarian cancer treatment in a subject, said method comprising measuring the expression level of an ovarian tumor marker gene in said subject after treatment of said subject, wherein a modulation in said expression level of said ovarian tumor marker gene in said subject, relative to the expression level of said ovarian tumor marker gene in said subject prior to said treatment, indicates an effective ovarian cancer treatment in said subject.

4. The method of claim 1, 2, or 3, wherein said expression level of said ovarian tumor marker gene is determined in said subject by measuring the expression level of said tumor marker gene in a sample from said subject.

5. The method of claim 4, wherein said sample from said subject is selected from the group consisting of a tissue biopsy, ovarian epithelial cell scrapings, peritoneal fluid, blood, urine, and serum.

6. The method of claim 1, 2, or 3, wherein said expression level of said tumor marker gene is measured *in vivo* in said subject.

7. The method of claim 1, 2, or 3, wherein said expression level of said tumor marker gene is determined by measuring the level of ovarian tumor marker mRNA.

8. The method of claim 7, wherein said level of ovarian tumor marker mRNA is measured using RT-PCR, Northern hybridization, dot-blotting, or *in situ* hybridization.

9. The method of claim 1, 2, or 3, wherein said expression level of said ovarian tumor marker gene is determined by measuring the level of ovarian tumor marker polypeptide encoded by said ovarian tumor marker gene.

10. The method of claim 9, wherein said level of ovarian tumor marker polypeptide is measured by ELISA, immunoblotting, or immunohistochemistry.

11. The method of claim 1, 2, or 3, wherein said expression level of said tumor marker gene is compared to the expression level of said tumor marker gene in a reference subject diagnosed with ovarian cancer.

12. The method of claim 2, wherein said expression level of said ovarian tumor marker gene in said subject is compared to the expression level of said tumor marker gene in a reference subject that is identified as having an increased risk for developing ovarian cancer.

13. A method of identifying a tumor as an ovarian tumor, said method comprising measuring the expression level of an ovarian tumor marker gene in a tumor cell from said tumor, wherein an increase in said expression level of said ovarian tumor marker gene in said tumor cell, relative to the expression level of said ovarian tumor marker gene in a noncancerous ovarian cell, identifies the tumor as an ovarian tumor.

14. A method of treating or preventing an ovarian tumor in a subject, said method comprising modulating production or activity of a polypeptide encoded by an ovarian tumor marker gene in an ovarian epithelial cell in said subject.

15. A method of inhibiting the growth or metastasis of an ovarian tumor cell in a subject, said method comprising modulating production or activity of a polypeptide encoded by an ovarian tumor marker gene in said ovarian tumor cell in said subject.

16. A method of inhibiting the growth or metastasis of an ovarian tumor in a subject, said method comprising contacting an ovarian tumor cell with an antibody that specifically binds an ovarian tumor marker polypeptide encoded by an ovarian tumor marker gene, wherein the binding of said antibody to said ovarian tumor marker polypeptide inhibits the growth or metastasis of said ovarian tumor in said subject.

17. The method of claim 16, wherein said ovarian tumor marker polypeptide is on the surface of said ovarian tumor cell.

18. The method of claim 16, wherein said antibody is coupled to a radioisotope or a toxic compound.

19. A method of diagnosing ovarian cancer in a subject, said method comprising measuring the amount of an ovarian tumor marker polypeptide in said subject, wherein an

amount of ovarian tumor marker polypeptide that is greater than the amount of ovarian tumor marker polypeptide measured in a subject not having ovarian cancer diagnoses an ovarian cancer in the subject.

20. The method of claim 19, wherein said ovarian tumor marker polypeptide is present at the surface of a cell.

21. The method of claim 19, wherein said ovarian tumor marker polypeptide is in soluble form.

22. The method of claim 1, 2, 3, 13, 14, 15, 16, or 19, wherein said ovarian tumor marker gene is selected from the group consisting of alpha prothymosin; beta polypeptide 2-like G protein subunit 1; Lutheran blood group (B-CAM); tumor rejection antigen-1 (gp96)1; HSP90; HSP60; Hepatoma-Derived Growth Factor (HGDF); DKFZp5860031; CD63 antigen (melanoma 1 antigen); protein kinase C substrate 80K-H; Polymerase II cofactor 4 (PC4); mitochondrial Tu translation elongation factor; hNRP H1; Solute carrier family 2; KIAA0591 protein; X-ray repair protein; DKFZP564M2423 protein; growth factor-regulated tyrosine kinase substrate; and eIF-2-associated p67.

23. The method of claim 1, 2, 3, 13, 14, 15, 16, or 19, wherein said ovarian tumor marker gene is selected from the group consisting of HLA-DR alpha chain; cysteine-rich protein 1; claudin 4; claudin 3; ceruloplasmin (ferroxidase); glutathione perroxidase 3; secretory leukocyte protease inhibitor; HOST-1 (FLJ14303 fis); interferon-induced transmembrane protein 1; apolipoprotein J/clusterin; serine protease inhibitor, Kunitz type 2; apoplipoprotein E; complement component 1, r subcomponent; G1P3/IFI-6-16; Lutheran blood group (BCAM); collagen type III, alpha-1; Mal (T cell differentiation protein); collagen type I, alpha-2; HLA-DPB1; bone marrow stroma antigen 2 (BST-2); or HLA-Cw.

24. The method of claim 1, 2, 3, 13, 14, 15, 16, or 19, wherein said ovarian tumor marker gene is selected from the group consisting of HOST-3 (Claudin-16); HOST-4; or HOST-5 (sodium dependent transporter isoform NaPi-Iib).

25. The method of claim 1, 2, 3, 13, 14, 15, 16, or 19, wherein said ovarian tumor marker gene comprises a nucleotide sequence set forth in one of SEQ ID NOs: 84-102.

26. The method of claim 1, 2, 3, 13, 14, 15, 16, or 19, wherein said ovarian tumor marker gene comprises a nucleotide sequence set forth in one of SEQ ID NOs: 103-129.

27. The method of claim 1, 2, 3, 13, 14, 15, 16, or 19, wherein said ovarian tumor marker gene comprises a nucleotide sequence set forth in one of SEQ ID NOs: 141, 143, or 145.

28. The method of claim 1, 2, 3, 13, 14, 15, 16, or 19, wherein said ovarian tumor is an epithelial ovarian tumor.

29. The method of claim 28, wherein said epithelial ovarian tumor is selected from the group consisting of a serous cystadenoma, a borderline serous tumor, a serous cystadenocarcinoma, a mucinous cystadenoma, a borderline mucinous tumor, a mucinous cystadenocarcinoma, an endometrioid carcinoma, an undifferentiated carcinoma, a clear cell adenocarcinoma, a cystadenofibroma, an adenofibroma, and a Brenner tumor.

30. A kit comprising an antibody for measuring the expression level of an ovarian tumor marker gene in a subject.

31. A kit comprising a nucleic acid for measuring the expression level of an ovarian tumor marker gene in a subject.

32. The kit of claim 30 or 31, wherein said ovarian tumor marker gene is selected from the group consisting of alpha prothymosin; beta polypeptide 2-like G protein subunit 1; Lutheran blood group (B-CAM); tumor rejection antigen-1 (gp96)1; HSP90; HSP60; Hepatoma-Derived Growth Factor (HGDF); DKFZp5860031; CD63 antigen (melanoma 1 antigen); protein kinase C substrate 80K-H; Polymerase II cofactor 4 (PC4); mitochondrial Tu translation elongation factor; hNRP H1; Solute carrier family 2; KIAA0591 protein; X-ray repair protein; DKFZP564M2423 protein; growth factor-regulated tyrosine kinase substrate; and eIF-2-associated p67.

33. The kit of claim 30 or 31, wherein said ovarian tumor marker gene is selected from the group consisting of HLA-DR alpha chain; cysteine-rich protein 1; claudin 4; claudin 3; ceruloplasmin (ferroxidase); glutathione perroxidase 3; secretory leukocyte protease inhibitor; HOST-1 (FLJ14303 fis); interferon-induced transmembrane protein 1; apolipoprotein J/clusterin; serine protease inhibitor, Kunitz type 2; apoplipoprotein E; complement component 1, r subcomponent; G1P3/IFI-6-16; Lutheran blood group (BCAM); collagen type III, alpha-1; Mal (T cell differentiation protein); collagen type I, alpha-2; HLA-DPB1; bone marrow stroma antigen 2 (BST-2); or HLA-Cw.

34. The kit of claim 30 or 31, wherein said ovarian tumor marker gene is selected from the group consisting of HOST-3 (Claudin-16); HOST-4; or HOST-5 (sodium dependent transporter isoform NaPi-Iib).

35. The kit of claim 30 or 31, wherein said ovarian tumor marker gene comprises a nucleotide sequence set forth in one of SEQ ID NOs: 84-102.

36. The kit of claim 30 or 31, wherein said ovarian tumor marker gene comprises a nucleotide sequence set forth in one of SEQ ID NOs: 103-129.

37. The kit of claim 30 or 31, wherein said ovarian tumor marker gene comprises a nucleotide sequence set forth in one of SEQ ID NOs: 141, 143, or 145.

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gctttggtgg ccagccagta cggatggtct ggcaacatgg agagaatcat gaaagcacaa 2100
gcgtaccaaa cgggcaagga catctctaca aattactatg cgagtcagaa gaaaacattt 2160
gaaattaatc ccagacaccc gctgatcaga gacatgcttc gacgaattaa ggaagatgaa 2220
gatgataaaa cagttttgga tcttgctgtg gttttgtttg aaacagcaac gcttcggtca 2280
gggtatcttt taccagacac taaagcatat ggagatagaa tagaaagaat gcttcgcctc 2340
agtttgaaca ttgaccctga tgcaaaggtg gaagaagagc ccgaagaaga acctgaagag 2400
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atactctcac catttggatc ctgtgtggag agggaatgtg aaatttacat catttctttt 2580
tgggagagac ttgttttgga tgccccctaa tccccttctc ccctgcactg taaaatgtgg 2640
gattatgggt cacaggaaaa agtgggtttt ttagttgaat tttttttaac attcctcatg 2700
aatgtaaatt tgtactattt aactgactat tcttgatgta aaatcttgtc atgtgtataa 2760
aaataaaaaa gatcccaaat 2780

<210> 8
<211> 838
<212> PRT
<213> Homo sapiens

<400> 8
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20 25 30
Pro His Ala Met Arg Ala Leu Trp Val Leu Gly Leu Cys Cys Val Leu
35 40 45
Leu Thr Phe Gly Ser Val Arg Ala Asp Asp Glu Val Asp Val Asp Gly
50 55 60
Thr Val Glu Glu Asp Leu Gly Lys Ser Arg Glu Gly Ser Arg Thr Asp
65 70 75 80
Asp Glu Val Val Gln Arg Glu Glu Glu Ala Ile Gln Leu Asp Gly Leu
85 90 95
Asn Ala Ser Gln Ile Arg Glu Leu Arg Glu Lys Ser Glu Lys Phe Ala
100 105 110
Phe Gln Ala Glu Val Asn Arg Met Met Lys Leu Ile Ile Asn Ser Leu
115 120 125
Tyr Lys Asn Lys Glu Ile Phe Leu Arg Glu Leu Ile Ser Asn Ala Ser
130 135 140
Asp Ala Leu Asp Lys Ile Arg Leu Ile Ser Leu Thr Asp Glu Asn Ala
145 150 155 160
Leu Ser Gly Asn Glu Glu Leu Thr Val Lys Ile Lys Cys Asp Lys Glu
165 170 175
Lys Asn Leu Leu His Val Thr Asp Thr Gly Val Gly Met Thr Arg Glu
180 185 190
Glu Leu Val Lys Asn Leu Gly Thr Ile Ala Lys Ser Gly Thr Ser Glu
195 200 205
Phe Leu Asn Lys Met Thr Glu Ala Gln Glu Asp Gly Gln Ser Thr Ser
210 215 220
Glu Leu Ile Gly Gln Phe Gly Val Gly Phe Tyr Ser Ala Phe Leu Val
225 230 235 240
Ala Asp Lys Val Ile Val Thr Ser Lys His Asn Asn Asp Thr Gln His
245 250 255

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Ile Trp Glu Ser Asp Ser Asn Glu Phe Ser Val Ile Ala Asp Pro Arg
            260                 265                 270
Gly Asn Thr Leu Gly Arg Gly Thr Thr Ile Thr Leu Val Leu Lys Glu
        275                 280                 285
Glu Ala Ser Asp Tyr Leu Glu Leu Asp Thr Ile Lys Asn Leu Val Lys
    290                 295                 300
Lys Tyr Ser Gln Phe Ile Asn Phe Pro Ile Tyr Val Trp Ser Ser Lys
305                 310                 315                 320
Thr Glu Thr Val Glu Glu Pro Met Glu Glu Glu Glu Ala Ala Lys Glu
                325                 330                 335
Glu Lys Glu Glu Ser Asp Asp Glu Ala Ala Val Glu Glu Glu Glu Glu
            340                 345                 350
Glu Lys Lys Pro Lys Thr Lys Lys Val Glu Lys Thr Val Trp Asp Trp
        355                 360                 365
Glu Leu Met Asn Asp Ile Lys Pro Ile Trp Gln Arg Pro Ser Lys Glu
    370                 375                 380
Val Glu Glu Asp Glu Tyr Lys Ala Phe Tyr Lys Ser Phe Ser Lys Glu
385                 390                 395                 400
Ser Asp Asp Pro Met Ala Tyr Ile His Phe Thr Ala Glu Gly Glu Val
                405                 410                 415
Thr Phe Lys Ser Ile Leu Phe Val Pro Thr Ser Ala Pro Arg Gly Leu
            420                 425                 430
Phe Asp Glu Tyr Gly Ser Lys Lys Ser Asp Tyr Ile Lys Leu Tyr Val
        435                 440                 445
Arg Arg Val Phe Ile Thr Asp Asp Phe His Asp Met Met Pro Lys Tyr
    450                 455                 460
Leu Asn Phe Val Lys Gly Val Val Asp Ser Asp Asp Leu Pro Leu Asn
465                 470                 475                 480
Val Ser Arg Glu Thr Leu Gln Gln His Lys Leu Leu Lys Val Ile Arg
                485                 490                 495
Lys Lys Leu Val Arg Lys Thr Leu Asp Met Ile Lys Lys Ile Ala Asp
            500                 505                 510
Asp Lys Tyr Asn Asp Thr Phe Trp Lys Glu Phe Gly Thr Asn Ile Lys
        515                 520                 525
Leu Gly Val Ile Glu Asp His Ser Asn Arg Thr Arg Leu Ala Lys Leu
    530                 535                 540
Leu Arg Phe Gln Ser Ser His His Pro Thr Asp Ile Thr Ser Leu Asp
545                 550                 555                 560
Gln Tyr Val Glu Arg Met Lys Glu Lys Gln Asp Lys Ile Tyr Phe Met
                565                 570                 575
Ala Gly Ser Ser Arg Lys Glu Ala Glu Ser Ser Pro Phe Val Glu Arg
            580                 585                 590
Leu Leu Lys Lys Gly Tyr Glu Val Ile Tyr Leu Thr Glu Pro Val Asp
        595                 600                 605
Glu Tyr Cys Ile Gln Ala Leu Pro Glu Phe Asp Gly Lys Arg Phe Gln
    610                 615                 620
Asn Val Ala Lys Glu Gly Val Lys Phe Asp Glu Ser Glu Lys Thr Lys
625                 630                 635                 640
Glu Ser Arg Glu Ala Val Glu Lys Glu Phe Glu Pro Leu Leu Asn Trp
                645                 650                 655
Met Lys Asp Lys Ala Leu Lys Asp Lys Ile Glu Lys Ala Val Val Ser
            660                 665                 670
Gln Arg Leu Thr Glu Ser Pro Cys Ala Leu Val Ala Ser Gln Tyr Gly
        675                 680                 685
Trp Ser Gly Asn Met Glu Arg Ile Met Lys Ala Gln Ala Tyr Gln Thr
    690                 695                 700
Gly Lys Asp Ile Ser Thr Asn Tyr Tyr Ala Ser Gln Lys Lys Thr Phe
705                 710                 715                 720
Glu Ile Asn Pro Arg His Pro Leu Ile Arg Asp Met Leu Arg Arg Ile
                725                 730                 735
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Lys Glu Asp Glu Asp Asp Lys Thr Val Leu Asp Leu Ala Val Val Leu
            740                 745                 750
Phe Glu Thr Ala Thr Leu Arg Ser Gly Tyr Leu Leu Pro Asp Thr Lys
        755                 760                 765
Ala Tyr Gly Asp Arg Ile Glu Arg Met Leu Arg Leu Ser Leu Asn Ile
    770                 775                 780
Asp Pro Asp Ala Lys Val Glu Glu Glu Pro Glu Glu Glu Pro Glu Glu
785                 790                 795                 800
Thr Ala Glu Asp Thr Thr Glu Asp Thr Glu Gln Asp Glu Asp Glu Glu
                805                 810                 815
Met Asp Val Gly Thr Asp Glu Glu Glu Glu Thr Ala Lys Glu Ser Thr
            820                 825                 830
Ala Glu Lys Asp Glu Leu
        835
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<210> 9
<211> 2912
<212> DNA
<213> Homo sapiens

<400> 9

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atgcctgagg aaacccagac ccaagaccaa ccgatggagg aggaggaggt tgagacgttc     120
gcctttcagg cagaaattgc ccagttgatg tcattgatca tcaatacttt ctactcgaac     180
aaagagatct ttctgagaga gctcatttca aattcatcag atgcattgga caaaatccgg     240
tatgaaactt tgacagatcc cagtaaatta gactctggga aagagctgca tattaacctt     300
ataccgaaca aacaagatcg aactctcact attgtggata ctggaattgg aatgaccaag     360
gctgacttga tcaataacct tggtactatc gccaagtctg ggaccaaagc gttcatggaa     420
gctttgcagg ctggtgcaga tatctctatg attggccagt tcggtgttgg tttttattct     480
gcttatttgg ttgctgagaa agtaactgtg atcaccaaac ataacgatga tgagcagtac     540
gcttgggagt cctcagcagg gggatcattc acagtgagga cagacacagg tgaacctatg     600
ggtcgtggaa caaaagttat cctacacctg aaagaagacc aaactgagta cttggaggaa     660
cgaagaataa aggagattgt gaagaaacat tctcagttta ttggatatcc cattactctt     720
tttgtggaga aggaacgtga taaagaagta agcgatgatg aggctgaaga aaaggaagac     780
aaagaagaag aaaaagaaaa agaagagaaa gagtcggaag acaaacctga aattgaagat     840
gttggttctg atgaggaaga agaaaagaag gatggtgaca agaagaagaa gaagaagatt     900
aaggaaaagt acatcgatca agaagagctc aacaaaacaa agcccatctg gaccagaaat     960
cccgacgata ttactaatga ggagtacgga gaattctata agagcttgac caatgactgg    1020
gaagatcact tggcagtgaa gcatttttca gttgaaggac agttggaatt cagagccctt    1080
ctatttgtcc cacgacgtgc tcctttttgat ctgtttgaaa acagaaagaa aaagaacaat    1140
atcaaattgt atgtacgcag agttttcatc atggataact gtgaggagct aatccctgaa    1200
tatctgaact tcattagagg ggtggtagac tcggaggatc tccctctaaa catatcccgt    1260
gagatgttgc aacaaagcaa aattttgaaa gttatcagga agaatttggt caaaaaatgc    1320
ttagaactct ttactgaact ggcggaagat aaagagaact acaagaaatt ctatgagcag    1380
ttctctaaaa acataaagct tggaatacac gaagactctc aaaatcggaa gaagctttca    1440
gagctgttaa ggtactacac atctgcctct ggtgatgaga tggtttctct caaggactac    1500
tgcaccagaa tgaaggagaa ccagaaacat atctattata tcacaggtga gaccaaggac    1560
caggtagcta actcagcctt tgtggaacgt cttcggaaac atggcttaga agtgatctat    1620
atgattgagc ccattgatga gtactgtgtc caacagctga aggaatttga ggggaagact    1680
ttagtgtcag tcaccaaaga aggcctggaa cttccagagg atgaagaaga gaaaaagaag    1740
caggaagaga aaaaaacaaa gtttgagaac ctctgcaaaa tcatgaaaga catattggag    1800
aaaaaagttg aaaaggtggt tgtgtcaaac cgattggtga catctccatg ctgtattgtc    1860
acaagcacat atggctggac agcaaacatg gagagaatca tgaaagctca agccctaaga    1920
gacaactcaa caatgggtta catggcagca aagaaacacc tggagataaa ccctgaccat    1980
tccattattg agaccttaag gcaaaaggca gaggctgata agaacgacaa gtctgtgaag    2040
gatctggtca tcttgcttta tgaaactgcg ctcctgtctt ctggcttcag tctggaagat    2100
ccccagacac atgctaacag gatctacagg atgatcaaac ttggtctggg tattgatgaa    2160
gatgacccta ctgctgatga taccagtgct gctgtaactg aagaaatgcc acccccttgaa   2220
ggagatgacg acacatcacg catggaagaa gtagactaat ctctggctga gggatgactt    2280
acctgttcag tactctacaa ttcctctgat aatatatttt caaggatgtt tttctttatt    2340
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tttgttaata ttaaaaagtc tgtatggcat gacaactact ttaaggggaa gataagattt 2400
ctgtctacta agtgatgctg tgatacctta ggcactaaag cagagctagt aatgcttttt 2460
gagtttcatg ttggttcttt cacagatggg gtaacgtgca ctgtaagacg tatgtaacat 2520
gatgttaact ttgtgtggtc taaagtgttt agctgtcaag ccggatgcct aagtagacca 2580
aatcttgtta ttgaagtgtt ctgagctgta tcttgatgtt tagaaaagta ttcgttacat 2640
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gtcctctaga aataggttaa actgaagcaa cttgatggaa ggatctctcc acagggcttg 2760
ttttccaaag aaaagtattg tttggaggag caaagttaaa agcctaccta agcatatcgt 2820
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<210> 10
<211> 732
<212> PRT
<213> Homo sapiens

<400> 10
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Ile Ile Asn Thr Phe Tyr Ser Asn Lys Glu Ile Phe Leu Arg Glu Leu
35 40 45
Ile Ser Asn Ser Ser Asp Ala Leu Asp Lys Ile Arg Tyr Glu Thr Leu
50 55 60
Thr Asp Pro Ser Lys Leu Asp Ser Gly Lys Glu Leu His Ile Asn Leu
65 70 75 80
Ile Pro Asn Lys Gln Asp Arg Thr Leu Thr Ile Val Asp Thr Gly Ile
85 90 95
Gly Met Thr Lys Ala Asp Leu Ile Asn Asn Leu Gly Thr Ile Ala Lys
100 105 110
Ser Gly Thr Lys Ala Phe Met Glu Ala Leu Gln Ala Gly Ala Asp Ile
115 120 125
Ser Met Ile Gly Gln Phe Gly Val Gly Phe Tyr Ser Ala Tyr Leu Val
130 135 140
Ala Glu Lys Val Thr Val Ile Thr Lys His Asn Asp Asp Glu Gln Tyr
145 150 155 160
Ala Trp Glu Ser Ser Ala Gly Gly Ser Phe Thr Val Arg Thr Asp Thr
165 170 175
Gly Glu Pro Met Gly Arg Gly Thr Lys Val Ile Leu His Leu Lys Glu
180 185 190
Asp Gln Thr Glu Tyr Leu Glu Glu Arg Arg Ile Lys Glu Ile Val Lys
195 200 205
Lys His Ser Gln Phe Ile Gly Tyr Pro Ile Thr Leu Phe Val Glu Lys
210 215 220
Glu Arg Asp Lys Glu Val Ser Asp Asp Glu Ala Glu Glu Lys Glu Asp
225 230 235 240
Lys Glu Glu Glu Lys Glu Lys Glu Glu Lys Glu Ser Glu Asp Lys Pro
245 250 255
Glu Ile Glu Asp Val Gly Ser Asp Glu Glu Glu Glu Lys Lys Asp Gly
260 265 270
Asp Lys Lys Lys Lys Lys Lys Ile Lys Glu Lys Tyr Ile Asp Gln Glu
275 280 285
Glu Leu Asn Lys Thr Lys Pro Ile Trp Thr Arg Asn Pro Asp Asp Ile
290 295 300
Thr Asn Glu Glu Tyr Gly Glu Phe Tyr Lys Ser Leu Thr Asn Asp Trp
305 310 315 320
Glu Asp His Leu Ala Val Lys His Phe Ser Val Glu Gly Gln Leu Glu
325 330 335

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Phe Arg Ala Leu Leu Phe Val Pro Arg Arg Ala Pro Phe Asp Leu Phe
            340                 345                 350
Glu Asn Arg Lys Lys Lys Asn Asn Ile Lys Leu Tyr Val Arg Arg Val
        355                 360                 365
Phe Ile Met Asp Asn Cys Glu Glu Leu Ile Pro Glu Tyr Leu Asn Phe
    370                 375                 380
Ile Arg Gly Val Val Asp Ser Glu Asp Leu Pro Leu Asn Ile Ser Arg
385                 390                 395                 400
Glu Met Leu Gln Gln Ser Lys Ile Leu Lys Val Ile Arg Lys Asn Leu
                405                 410                 415
Val Lys Lys Cys Leu Glu Leu Phe Thr Glu Leu Ala Glu Asp Lys Glu
            420                 425                 430
Asn Tyr Lys Lys Phe Tyr Glu Gln Phe Ser Lys Asn Ile Lys Leu Gly
        435                 440                 445
Ile His Glu Asp Ser Gln Asn Arg Lys Lys Leu Ser Glu Leu Leu Arg
    450                 455                 460
Tyr Tyr Thr Ser Ala Ser Gly Asp Glu Met Val Ser Leu Lys Asp Tyr
465                 470                 475                 480
Cys Thr Arg Met Lys Glu Asn Gln Lys His Ile Tyr Tyr Ile Thr Gly
                485                 490                 495
Glu Thr Lys Asp Gln Val Ala Asn Ser Ala Phe Val Glu Arg Leu Arg
            500                 505                 510
Lys His Gly Leu Glu Val Ile Tyr Met Ile Glu Pro Ile Asp Glu Tyr
        515                 520                 525
Cys Val Gln Gln Leu Lys Glu Phe Glu Gly Lys Thr Leu Val Ser Val
    530                 535                 540
Thr Lys Glu Gly Leu Glu Leu Pro Glu Asp Glu Glu Glu Lys Lys Lys
545                 550                 555                 560
Gln Glu Glu Lys Lys Thr Lys Phe Glu Asn Leu Cys Lys Ile Met Lys
                565                 570                 575
Asp Ile Leu Glu Lys Lys Val Glu Lys Val Val Val Ser Asn Arg Leu
            580                 585                 590
Val Thr Ser Pro Cys Cys Ile Val Thr Ser Thr Tyr Gly Trp Thr Ala
        595                 600                 605
Asn Met Glu Arg Ile Met Lys Ala Gln Ala Leu Arg Asp Asn Ser Thr
    610                 615                 620
Met Gly Tyr Met Ala Ala Lys Lys His Leu Glu Ile Asn Pro Asp His
625                 630                 635                 640
Ser Ile Ile Glu Thr Leu Arg Gln Lys Ala Glu Ala Asp Lys Asn Asp
                645                 650                 655
Lys Ser Val Lys Asp Leu Val Ile Leu Leu Tyr Glu Thr Ala Leu Leu
            660                 665                 670
Ser Ser Gly Phe Ser Leu Glu Asp Pro Gln Thr His Ala Asn Arg Ile
        675                 680                 685
Tyr Arg Met Ile Lys Leu Gly Leu Gly Ile Asp Glu Asp Asp Pro Thr
    690                 695                 700
Ala Asp Asp Thr Ser Ala Ala Val Thr Glu Glu Met Pro Pro Leu Glu
705                 710                 715                 720
Gly Asp Asp Asp Thr Ser Arg Met Glu Glu Val Asp
                725                 730

<210> 11
<211> 2227
<212> DNA
<213> Homo sapiens

<400> 11
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acagtctttc gccagatgag accggtgtcc agggtactgg ctcctcatct cactcgggct     120
tatgccaaag atgtaaaatt tggtgcagat gcccgagcct taatgcttca aggtgtagac     180
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cttttagccg atgctgtggc cgttacaatg gggccaaagg gaagaacagt gattattgag     240
cagagttggg gaagtcccaa agtaacaaaa gatggtgtga ctgttgcaaa gtcaattgac     300
ttaaaagata aatacaagaa cattggagct aaacttgttc aagatgttgc caataacaca     360
aatgaagaag ctggggatgg cactaccact gctactgtac tggcacgctc tatagccaag     420
gaaggcttcg agaagattag caaaggtgct aatccagtgg aaatcaggag aggtgtgatg     480
ttagctgttg atgctgtaat tgctgaactt aaaaagcagt ctaaacctgt gaccacccct     540
gaagaaattg cacaggttgc tacgatttct gcaaacggag acaaagaaat tggcaatatc     600
atctctgatg caatgaaaaa agttggaaga aagggtgtca tcacagtaaa ggatggaaaa     660
acactgaatg atgaattaga aattattgaa ggcatgaagt ttgatcgagg ctatatttct     720
ccatacttta ttaatacatc aaaaggtcag aaatgtgaat tccaggatgc ctatgttctg     780
ttgagtgaaa agaaaatttc tagtatccag tccattgtac ctgctcttga aattgccaat     840
gctcaccgta agcctttggt cataatcgct gaagatgttg atggagaagc tctaagtaca     900
ctcgtcttga ataggctaaa ggttggtctt caggttgtgg cagtcaaggc tccagggttt     960
ggtgacaata gaaagaacca gcttaaagat atggctattg ctactggtgg tgcagtgttt    1020
ggagaagagg gattgaccct gaatcttgaa gacgttcagc ctcatgactt aggaaaagtt    1080
ggagaggtca ttgtgaccaa agacgatgcc atgctcttaa aaggaaaagg tgacaaggct    1140
caaattgaaa aacgtattca agaaatcatt gagcagttag atgtcacaac tagtgaatat    1200
gaaaaggaaa aactgaatga acggcttgca aaactttcag atggagtggc tgtgctgaag    1260
gttggtggga caagtgatgt tgaagtgaat gaaaagaaag acagagttac agatgccctt    1320
aatgctacaa gagctgctgt tgaagaaggc attgttttgg gagggggttg tgccctcctt    1380
cgatgcattc cagccttgga ctcattgact ccagctaatg aagatcaaaa aattggtata    1440
gaaattatta aaagaacact caaaattcca gcaatgacca ttgctaagaa tgcaggtgtt    1500
gaaggatctt tgatagttga gaaaattatg caaagttcct cagaagttgg ttatgatgct    1560
atggctggag attttgtgaa tatggtggaa aaaggaatca ttgacccaac aaaggttgtg    1620
agaactgctt tattggatgc tgctggtgtg gcctctctgt taactacagc agaagttgta    1680
gtcacagaaa ttcctaaaga agagaaggac cctggaatgg gtgcaatggg tggaatggga    1740
ggtggtatgg gaggtggcat gttctaactc ctagactagt gctttacctt tattaatgaa    1800
ctgtgacagg aagcccaagg cagtgttcct caccaataac ttcagagaag tcagttggag    1860
aaaatgaaga aaaaggctgg ctgaaaatca ctataaccat cagttactgg tttcagttga    1920
caaaatatat aatggtttac tgctgtcatt gtccatgcct acagataatt tattttgtat    1980
ttttgaataa aaaacatttg tacattcctg atactgggta caagagccat gtaccagtgt    2040
actgctttca acttaaatca ctgaggcatt tttactacta ttctgttaaa atcaggattt    2100
tagtgcttgc caccaccaga tgagaagtta agcagccttt ctgtggagag tgagaataat    2160
tgtgtacaaa gtagagaagt atccaattat gtgacaacct ttgtgtaata aaaatttgtt    2220
taaagtt                                                              2227

<210> 12
<211> 573
<212> PRT
<213> Homo sapiens

<400> 12
Met Leu Arg Leu Pro Thr Val Phe Arg Gln Met Arg Pro Val Ser Arg
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Val Leu Ala Pro His Leu Thr Arg Ala Tyr Ala Lys Asp Val Lys Phe
            20                  25                  30
Gly Ala Asp Ala Arg Ala Leu Met Leu Gln Gly Val Asp Leu Leu Ala
        35                  40                  45
Asp Ala Val Ala Val Thr Met Gly Pro Lys Gly Arg Thr Val Ile Ile
    50                  55                  60
Glu Gln Ser Trp Gly Ser Pro Lys Val Thr Lys Asp Gly Val Thr Val
65                  70                  75                  80
Ala Lys Ser Ile Asp Leu Lys Asp Lys Tyr Lys Asn Ile Gly Ala Lys
                85                  90                  95
Leu Val Gln Asp Val Ala Asn Asn Thr Asn Glu Glu Ala Gly Asp Gly
            100                 105                 110
Thr Thr Thr Ala Thr Val Leu Ala Arg Ser Ile Ala Lys Glu Gly Phe
        115                 120                 125
Glu Lys Ile Ser Lys Gly Ala Asn Pro Val Glu Ile Arg Arg Gly Val
    130                 135                 140
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Met Leu Ala Val Asp Ala Val Ile Ala Glu Leu Lys Lys Gln Ser Lys
145                 150                 155                 160
Pro Val Thr Thr Pro Glu Glu Ile Ala Gln Val Ala Thr Ile Ser Ala
                165                 170                 175
Asn Gly Asp Lys Glu Ile Gly Asn Ile Ile Ser Asp Ala Met Lys Lys
            180                 185                 190
Val Gly Arg Lys Gly Val Ile Thr Val Lys Asp Gly Lys Thr Leu Asn
        195                 200                 205
Asp Glu Leu Glu Ile Ile Glu Gly Met Lys Phe Asp Arg Gly Tyr Ile
    210                 215                 220
Ser Pro Tyr Phe Ile Asn Thr Ser Lys Gly Gln Lys Cys Glu Phe Gln
225                 230                 235                 240
Asp Ala Tyr Val Leu Leu Ser Glu Lys Lys Ile Ser Ser Ile Gln Ser
                245                 250                 255
Ile Val Pro Ala Leu Glu Ile Ala Asn Ala His Arg Lys Pro Leu Val
            260                 265                 270
Ile Ile Ala Glu Asp Val Asp Gly Glu Ala Leu Ser Thr Leu Val Leu
        275                 280                 285
Asn Arg Leu Lys Val Gly Leu Gln Val Val Ala Val Lys Ala Pro Gly
    290                 295                 300
Phe Gly Asp Asn Arg Lys Asn Gln Leu Lys Asp Met Ala Ile Ala Thr
305                 310                 315                 320
Gly Gly Ala Val Phe Gly Glu Glu Gly Leu Thr Leu Asn Leu Glu Asp
                325                 330                 335
Val Gln Pro His Asp Leu Gly Lys Val Gly Glu Val Ile Val Thr Lys
            340                 345                 350
Asp Asp Ala Met Leu Leu Lys Gly Lys Gly Asp Lys Ala Gln Ile Glu
        355                 360                 365
Lys Arg Ile Gln Glu Ile Ile Glu Gln Leu Asp Val Thr Thr Ser Glu
    370                 375                 380
Tyr Glu Lys Glu Lys Leu Asn Glu Arg Leu Ala Lys Leu Ser Asp Gly
385                 390                 395                 400
Val Ala Val Leu Lys Val Gly Gly Thr Ser Asp Val Glu Val Asn Glu
                405                 410                 415
Lys Lys Asp Arg Val Thr Asp Ala Leu Asn Ala Thr Arg Ala Ala Val
            420                 425                 430
Glu Glu Gly Ile Val Leu Gly Gly Gly Cys Ala Leu Leu Arg Cys Ile
        435                 440                 445
Pro Ala Leu Asp Ser Leu Thr Pro Ala Asn Glu Asp Gln Lys Ile Gly
    450                 455                 460
Ile Glu Ile Ile Lys Arg Thr Leu Lys Ile Pro Ala Met Thr Ile Ala
465                 470                 475                 480
Lys Asn Ala Gly Val Glu Gly Ser Leu Ile Val Glu Lys Ile Met Gln
                485                 490                 495
Ser Ser Ser Glu Val Gly Tyr Asp Ala Met Ala Gly Asp Phe Val Asn
            500                 505                 510
Met Val Glu Lys Gly Ile Ile Asp Pro Thr Lys Val Val Arg Thr Ala
        515                 520                 525
Leu Leu Asp Ala Ala Gly Val Ala Ser Leu Leu Thr Thr Ala Glu Val
    530                 535                 540
Val Val Thr Glu Ile Pro Lys Glu Glu Lys Asp Pro Gly Met Gly Ala
545                 550                 555                 560
Met Gly Gly Met Gly Gly Gly Met Gly Gly Gly Met Phe
                565                 570
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<210> 13
<211> 2376
<212> DNA
<213> Homo sapiens

<400> 13
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attgaatttc aaacacaaac aactcgacga gcgcgcaccc accgcgccgg agccttgccc     120
cgatccgcgc ccgccccgtc cgtgcggcgc gcgggcggag acgccgtggc cgcgccggag     180
ctcgggccgg gggccaccat cgaggcgggg gccgcgcgag ggccggagcg gagcggcgcc     240
gccaccgccg cacgcgcaaa cttgggctcg cgcttcccgg cccggcgcgg agcccggggc     300
gcccggagcc ccgccatgtc gcgatccaac cggcagaagg agtacaaatg cggggacctg     360
gtgttcgcca agatgaaggg ctacccacac tggccggccc ggattgacga gatgcctgag     420
gctgccgtga aatcaacagc caacaaatac caagtctttt ttttcgggac ccacgagacg     480
gcattcctgg gccccaaaga cctcttccct tacgaggaat ccaaggagaa gtttggcaag     540
cccaacaaga ggaaagggtt cagcgagggg ctgtgggaga tcgagaacaa ccctactgtc     600
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<210> 14
<211> 240
<212> PRT
<213> Homo sapiens

<400> 14
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            20                  25                  30
Met Pro Glu Ala Ala Val Lys Ser Thr Ala Asn Lys Tyr Gln Val Phe
        35                  40                  45
Phe Phe Gly Thr His Glu Thr Ala Phe Leu Gly Pro Lys Asp Leu Phe
    50                  55                  60
Pro Tyr Glu Glu Ser Lys Glu Lys Phe Gly Lys Pro Asn Lys Arg Lys
65                  70                  75                  80
Gly Phe Ser Glu Gly Leu Trp Glu Ile Glu Asn Asn Pro Thr Val Lys
                85                  90                  95
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Ala Ser Gly Tyr Gln Ser Ser Gln Lys Lys Ser Cys Val Glu Glu Pro
100 105 110
Glu Pro Glu Pro Glu Ala Ala Glu Gly Asp Gly Asp Lys Lys Gly Asn
115 120 125
Ala Glu Gly Ser Ser Asp Glu Glu Gly Lys Leu Val Ile Asp Glu Pro
130 135 140
Ala Lys Glu Lys Asn Glu Lys Gly Ala Leu Lys Arg Arg Ala Gly Asp
145 150 155 160
Leu Leu Glu Asp Ser Pro Lys Arg Pro Lys Glu Ala Glu Asn Pro Glu
165 170 175
Gly Glu Glu Lys Glu Ala Ala Thr Leu Glu Val Glu Arg Pro Leu Pro
180 185 190
Met Glu Val Glu Lys Asn Ser Thr Pro Ser Glu Pro Gly Ser Gly Arg
195 200 205
Gly Pro Pro Gln Glu Glu Glu Glu Glu Glu Asp Glu Glu Glu Glu Ala
210 215 220
Thr Lys Glu Asp Ala Glu Ala Pro Gly Ile Arg Asp His Glu Ser Leu
225 230 235 240

<210> 15
<211> 3689
<212> DNA
<213> Homo sapiens

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aagaagagga agaagaccaa ggcccaccat gccccaggct cagcagggag ctgctggagg   2280
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gtttcatagg aggtaatcac cagacaactg cagaatgtag aacactgagc aggacaactg   3600
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<210> 16
<211> 921
<212> PRT
<213> Homo sapiens

<400> 16

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Leu Lys Gln Ala Glu Glu Leu Arg Gln Tyr Lys Val Leu Val His Ala
            20                  25                  30
Gln Glu Arg Glu Leu Thr Gln Leu Arg Glu Lys Leu Arg Glu Gly Arg
        35                  40                  45
Asp Ala Ser Arg Ser Leu Asn Glu His Leu Gln Ala Leu Leu Thr Pro
    50                  55                  60
Asp Glu Pro Asp Lys Ser Gln Gly Gln Asp Leu Gln Glu Gln Leu Ala
65                  70                  75                  80
Glu Gly Cys Arg Leu Ala Gln His Leu Val Gln Lys Leu Ser Pro Glu
                85                  90                  95
Asn Asp Asn Asp Asp Asp Glu Asp Val Gln Val Glu Val Ala Glu Lys
            100                 105                 110
Val Gln Lys Ser Ser Ala Pro Arg Glu Met Gln Lys Ala Glu Glu Lys
        115                 120                 125
Glu Val Pro Glu Asp Ser Leu Glu Glu Cys Ala Ile Thr Cys Ser Asn
    130                 135                 140
Ser His Gly Pro Tyr Asp Ser Asn Gln Pro His Arg Lys Thr Lys Ile
145                 150                 155                 160
Thr Phe Glu Glu Asp Lys Val Asp Ser Thr Leu Ile Gly Ser Ser Ser
                165                 170                 175
His Val Glu Trp Glu Asp Ala Val His Ile Ile Pro Glu Asn Glu Ser
            180                 185                 190
Asp Asp Glu Glu Glu Glu Glu Lys Gly Pro Val Ser Pro Arg Asn Leu
        195                 200                 205
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Gln Glu Ser Glu Glu Glu Glu Val Pro Gln Glu Ser Trp Asp Glu Gly
    210                 215                 220
Tyr Ser Thr Leu Ser Ile Pro Pro Glu Met Leu Ala Ser Tyr Lys Ser
225                 230                 235                 240
Tyr Ser Ser Thr Phe His Ser Leu Glu Glu Gln Gln Val Cys Met Ala
                245                 250                 255
Val Asp Ile Gly Arg His Arg Trp Asp Gln Val Lys Lys Glu Asp His
            260                 265                 270
Glu Ala Thr Gly Pro Arg Leu Ser Arg Glu Leu Leu Asp Glu Lys Gly
        275                 280                 285
Pro Glu Val Leu Gln Asp Ser Leu Asp Arg Cys Tyr Ser Thr Pro Ser
    290                 295                 300
Gly Cys Leu Glu Leu Thr Asp Ser Cys Gln Pro Tyr Arg Ser Ala Phe
305                 310                 315                 320
Tyr Val Leu Glu Gln Gln Arg Val Gly Leu Ala Val Asn Met Asp Glu
                325                 330                 335
Ile Glu Lys Tyr Gln Glu Val Glu Glu Asp Gln Asp Pro Ser Cys Pro
            340                 345                 350
Arg Leu Ser Arg Glu Leu Leu Asp Glu Lys Glu Pro Glu Val Leu Gln
        355                 360                 365
Asp Ser Leu Gly Arg Cys Tyr Ser Thr Pro Ser Gly Tyr Leu Glu Leu
    370                 375                 380
Pro Asp Leu Gly Gln Pro Tyr Ser Ser Ala Val Tyr Ser Leu Glu Glu
385                 390                 395                 400
Gln Tyr Leu Gly Leu Ala Leu Asp Val Asp Arg Ile Lys Lys Asp Gln
                405                 410                 415
Glu Glu Glu Glu Asp Gln Gly Pro Pro Cys Pro Arg Leu Ser Arg Glu
            420                 425                 430
Leu Leu Glu Val Val Glu Pro Glu Val Leu Gln Asp Ser Leu Asp Arg
        435                 440                 445
Cys Tyr Ser Thr Pro Ser Ser Cys Leu Glu Gln Pro Asp Ser Cys Gln
    450                 455                 460
Pro Tyr Gly Ser Ser Phe Tyr Ala Leu Glu Glu Lys His Val Gly Phe
465                 470                 475                 480
Ser Leu Asp Val Gly Glu Ile Glu Lys Lys Gly Lys Gly Lys Lys Arg
                485                 490                 495
Arg Gly Arg Arg Ser Lys Lys Glu Arg Arg Arg Gly Arg Lys Glu Gly
            500                 505                 510
Glu Glu Asp Gln Asn Pro Pro Cys Pro Arg Leu Ser Arg Glu Leu Leu
        515                 520                 525
Asp Glu Lys Gly Pro Glu Val Leu Gln Asp Ser Leu Asp Arg Cys Tyr
    530                 535                 540
Ser Thr Pro Ser Gly Cys Leu Glu Leu Thr Asp Ser Cys Gln Pro Tyr
545                 550                 555                 560
Arg Ser Ala Phe Tyr Ile Leu Glu Gln Gln Arg Val Gly Leu Ala Val
                565                 570                 575
Asp Met Asp Glu Ile Glu Lys Tyr Gln Glu Val Glu Glu Asp Gln Asp
            580                 585                 590
Pro Ser Cys Pro Arg Leu Ser Gly Glu Leu Leu Asp Glu Lys Glu Pro
        595                 600                 605
Glu Val Leu Gln Glu Ser Leu Asp Arg Cys Tyr Ser Thr Pro Ser Gly
    610                 615                 620
Cys L u Glu Leu Thr Asp Ser Cys Gln Pro Tyr Arg Ser Ala Phe Tyr
625                 630                 635                 640
Ile Leu Glu Gln Gln Arg Val Gly Leu Ala Val Asp Met Asp Glu Ile
                645                 650                 655
Glu Lys Tyr Gln Glu Val Glu Glu Asp Gln Asp Pro Ser Cys Pro Arg
            660                 665                 670
Leu Ser Arg Glu Leu Leu Asp Glu Lys Glu Pro Glu Val Leu Gln Asp
        675                 680                 685
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Ser Leu Gly Arg Cys Tyr Ser Thr Pro Ser Gly Tyr Leu Glu Leu Pro
690 695 700
Asp Leu Gly Gln Pro Tyr Ser Ser Ala Val Tyr Ser Leu Glu Glu Gln
705 710 715 720
Tyr Leu Gly Leu Ala Leu Asp Val Asp Arg Ile Lys Lys Asp Gln Glu
725 730 735
Glu Glu Glu Asp Gln Gly Pro Pro Cys Pro Arg Leu Ser Arg Glu Leu
740 745 750
Leu Glu Val Val Glu Pro Glu Val Leu Gln Asp Ser Leu Asp Arg Cys
755 760 765
Tyr Ser Thr Pro Ser Ser Cys Leu Glu Gln Pro Asp Ser Cys Gln Pro
770 775 780
Tyr Gly Ser Ser Phe Tyr Ala Leu Glu Glu Lys His Val Gly Phe Ser
785 790 795 800
Leu Asp Val Gly Glu Ile Glu Lys Lys Gly Lys Gly Lys Lys Arg Arg
805 810 815
Gly Arg Arg Ser Lys Lys Glu Arg Arg Arg Gly Arg Lys Glu Gly Glu
820 825 830
Glu Asp Gln Asn Pro Pro Cys Pro Arg Leu Asn Ser Met Leu Met Glu
835 840 845
Val Glu Glu Pro Glu Val Leu Gln Asp Ser Leu Asp Ile Cys Tyr Ser
850 855 860
Thr Pro Ser Met Tyr Phe Glu Leu Pro Asp Ser Phe Gln His Tyr Arg
865 870 875 880
Ser Val Phe Tyr Ser Phe Glu Glu Glu His Ile Ser Phe Ala Leu Tyr
885 890 895
Val Asp Asn Arg Phe Phe Thr Leu Thr Val Thr Ser Leu His Leu Val
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Phe Gln Met Gly Val Ile Phe Pro Gln
915 920

<210> 17
<211> 664
<212> DNA
<213> Homo sapiens

<400> 17
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cgactcccgc aaagggacaa ggttcctccc tctcctgcag agtaggcatc tgggcaccaa 540
gaccttccct caacagagga cactgagccc aacggagttc tgggatggga ggggtgggag 600
catgggaagg gaggcatccc acccccaaga agaactgaat aaagattgct gagcaaagga 660
aggc 664

<210> 18
<211> 138
<212> PRT
<213> Homo sapiens

<400> 18
Met Ile Leu Gln Gln Pro Leu Gln Arg Gly Pro Gln Gly Gly Ala Gln
1 5 10 15
Arg Leu Pro Arg Ala Ala Leu Gly Val Thr Trp Gly Leu Asp Ala Ser
20 25 30

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Ser Pro Leu Arg Gly Ala Val Pro Met Ser Thr Lys Arg Arg Leu Glu
        35                  40                  45
Glu Glu Gln Glu Pro Leu Arg Lys Gln Phe Leu Ser Glu Glu Asn Met
    50                  55                  60
Ala Thr His Phe Ser Gln Leu Ser Leu His Asn Asp His Pro Tyr Cys
65                  70                  75                  80
Ser Pro Pro Met Thr Phe Ser Pro Ala Leu Pro Pro Leu Arg Ser Pro
                85                  90                  95
Cys Ser Glu Leu Leu Leu Trp Arg Tyr Pro Gly Ser Leu Ile Pro Glu
            100                 105                 110
Ala Leu Arg Leu Leu Arg Leu Gly Asp Thr Pro Ser Pro Pro Tyr Pro
        115                 120                 125
Ala Thr Pro Ala Gly Asp Ile Met Glu Leu
    130                 135
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<210> 19
<211> 2056
<212> DNA
<213> Homo sapiens

<400> 19

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cgtgaagaca cagcgcatct ccccgctgta ggcttctccc acagaacccg tttcgggcct     120
cagagcgtct ggtgagatgc tgttgccgct gctgctgctg ctacccatgt gctgggccgt     180
ggaggtcaag aggccccggg gcgtctccct caccaatcat cacttctacg atgagtccaa     240
gcctttcacc tgcctggacg gttcggccac catcccattt gatcaggtca acgatgacta     300
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<210> 20
<211> 527
<212> PRT

<213> Homo sapiens

<400> 20
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            20   25   30
Glu Ser Lys Pro Phe Thr Cys Leu Asp Gly Ser Ala Thr Ile Pro Phe
        35   40   45
Asp Gln Val Asn Asp Asp Tyr Cys Asp Cys Lys Asp Gly Ser Asp Glu
    50   55   60
Pro Gly Thr Ala Ala Cys Pro Asn Gly Ser Phe His Cys Thr Asn Thr
65   70   75   80
Gly Tyr Lys Pro Leu Tyr Ile Pro Ser Asn Arg Val Asn Asp Gly Val
                85   90   95
Cys Asp Cys Cys Asp Gly Thr Asp Glu Tyr Asn Ser Gly Val Ile Cys
            100   105   110
Glu Asn Thr Cys Lys Glu Lys Gly Arg Lys Glu Arg Glu Ser Leu Gln
        115   120   125
Gln Met Ala Glu Val Thr Arg Glu Gly Phe Arg Leu Lys Lys Ile Leu
    130   135   140
Ile Glu Asp Trp Lys Lys Ala Arg Glu Glu Lys Gln Lys Lys Leu Ile
145   150   155   160
Glu Leu Gln Ala Gly Lys Lys Ser Leu Glu Asp Gln Val Glu Met Leu
                165   170   175
Arg Thr Val Lys Glu Glu Ala Glu Lys Pro Glu Arg Glu Ala Lys Glu
            180   185   190
Gln His Gln Lys Leu Trp Glu Glu Gln Leu Ala Ala Ala Lys Ala Gln
        195   200   205
Gln Glu Gln Glu Leu Ala Ala Asp Ala Phe Lys Glu Leu Asp Asp Asp
    210   215   220
Met Asp Gly Thr Val Ser Val Thr Glu Leu Gln Thr His Pro Glu Leu
225   230   235   240
Asp Thr Asp Gly Asp Gly Ala Leu Ser Glu Ala Glu Ala Gln Ala Leu
                245   250   255
Leu Ser Gly Asp Thr Gln Thr Asp Ala Thr Ser Phe Tyr Asp Arg Val
            260   265   270
Trp Ala Ala Ile Arg Asp Lys Tyr Arg Ser Glu Ala Leu Pro Thr Asp
        275   280   285
Leu Pro Ala Pro Ser Ala Pro Asp Leu Thr Glu Pro Lys Glu Glu Gln
    290   295   300
Pro Pro Val Pro Ser Ser Pro Thr Glu Glu Glu Glu Glu Glu Glu Glu
305   310   315   320
Glu Glu Glu Glu Ala Glu Glu Glu Glu Glu Glu Glu Asp Ser Glu Glu
                325   330   335
Ala Pro Pro Pro Leu Ser Pro Pro Gln Pro Ala Ser Pro Ala Glu Glu
            340   345   350
Asp Lys Met Pro Pro Tyr Asp Glu Gln Thr Gln Ala Phe Ile Asp Ala
        355   360   365
Ala Gln Glu Ala Arg Asn Lys Phe Glu Glu Ala Glu Arg Ser Leu Lys
    370   375   380
Asp Met Glu Glu Ser Ile Arg Asn Leu Glu Gln Glu Ile Ser Phe Asp
385   390   395   400
Phe Gly Pro Asn Gly Glu Phe Ala Tyr Leu Tyr Ser Gln Cys Tyr Glu
                405   410   415
Leu Thr Thr Asn Glu Tyr Val Tyr Arg Leu Cys Pro Phe Lys Leu Val
            420   425   430
Ser Gln Lys Pro Lys Leu Gly Gly Ser Pro Thr Ser Leu Gly Thr Trp
        435   440   445
Gly Ser Trp Ile Gly Pro Asp His Asp Lys Phe Ser Ala Met Lys Tyr

```
    450                 455                 460
Glu Gln Gly Thr Gly Cys Trp Gln Gly Pro Asn Arg Ser Thr Thr Val
465                 470                 475                 480
Arg Leu Leu Cys Gly Lys Glu Thr Met Val Thr Ser Thr Thr Glu Pro
                485                 490                 495
Ser Arg Cys Glu Tyr Leu Met Glu Leu Met Thr Pro Ala Ala Cys Pro
            500                 505                 510
Glu Pro Pro Pro Glu Ala Pro Thr Glu Asp Asp His Asp Glu Leu
        515                 520                 525
```

<210> 21
<211> 384
<212> DNA
<213> Homo sapiens

<400> 21

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atgcctaaat caaaggaact tgtttcttca agctcttctg gcagtgattc tgacagtgag      60
gttgacaaaa agttaaagag gaaaaagcaa gttgctccag aaaaacctgt aaagaaacaa     120
aagacaggtg agacttcgag agccctgtca tcttctaaac agagcagcag cagcagagat     180
gataacatgt ttcagattgg gaaaatgagg tacgttagtg ttcgcgattt taaaggcaaa     240
gtgctaattg atattagaga atattggatg gatcctgaag gtgaaatgaa accaggaaga     300
aaaggtattt ctttaaatcc agaacaatgg agccagctga aggaacagat ctctgatata     360
gatgacgcag taagaaagct gtga                                            384
```

<210> 22
<211> 127
<212> PRT
<213> Homo sapiens

<400> 22

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Met Pro Lys Ser Lys Glu Leu Val Ser Ser Ser Ser Ser Gly Ser Asp
1               5                   10                  15
Ser Asp Ser Glu Val Asp Lys Lys Leu Lys Arg Lys Lys Gln Val Ala
            20                  25                  30
Pro Glu Lys Pro Val Lys Lys Gln Lys Thr Gly Glu Thr Ser Arg Ala
        35                  40                  45
Leu Ser Ser Ser Lys Gln Ser Ser Ser Ser Arg Asp Asp Asn Met Phe
    50                  55                  60
Gln Ile Gly Lys Met Arg Tyr Val Ser Val Arg Asp Phe Lys Gly Lys
65                  70                  75                  80
Val Leu Ile Asp Ile Arg Glu Tyr Trp Met Asp Pro Glu Gly Glu Met
                85                  90                  95
Lys Pro Gly Arg Lys Gly Ile Ser Leu Asn Pro Glu Gln Trp Ser Gln
            100                 105                 110
Leu Lys Glu Gln Ile Ser Asp Ile Asp Asp Ala Val Arg Lys Leu
        115                 120                 125
```

<210> 23
<211> 1554
<212> DNA
<213> Homo sapiens

<400> 23

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gaccacaatg gcggccgcca ccctgctgcg cgcgacgccc cacttcagcg gtctcgccgc      60
cggccggacc ttcctgctgc agggtctgtt gcggctgctg aaagccccgg cattgcctct     120
cttgtgccgc ggcctggccg tggaggccaa gaagacttac gtgcgcgaca agccacatgt     180
gaatgtgggt accatcggcc atgtggacca cgggaagacc acgctgactg cagccatcac     240
gaagattcta gctgagggag gtggggctaa gttcaagaag tacgaggaga ttgacaatgc     300
cccggaggag cgagctcggg gtatcaccat caatgcggct catgtggagt atagcactgc     360
cgcccgccac tacgcccaca cagactgccc gggtcatgca gattatgtta agaatatgat     420
```

```
cacaggcact gcacccctcg acggctgcat cctggtggta gcagccaatg acggccccat     480
gccccagacc cgagagcact tattactggc cagacagatt ggggtggagc atgtggtggt     540
gtatgtgaac aaggctgacg ctgtccagga ctctgagatg gtggaactgg tggaactgga     600
gatccgggag ctgctcaccg agtttggcta taaaggggag gagaccccag tcatcgtagg     660
ctctgctctc tgtgcccttg agggtcggga ccctgagtta ggcctgaagt ctgtgcagaa     720
gctactggat gctgtggaca cttacatccc agtgcccgcc cgggacctgg agaagccttt     780
cctgctgcct gtggaggcgg tgtactccgt ccctggccgt ggcaccgtgg tgacaggtac     840
actagagcgt ggcattttaa agaagggaga cgagtgtgag ctcctaggac atagcaagaa     900
catccgcact gtggtgacag gcattgagat gttccacaag agcctggaga gggccgaggc     960
cggagataac ctcggggccc tggtccgagg cttgaagcgg gaggacttgc ggcggggcct    1020
ggtcatggtc aagccaggtt ccatcaagcc ccaccagaag gtggaggccc aggtttacat    1080
cctcagcaag gaggaaggtg gccgccacaa gccctttgtg tcccacttca tgcctgtcat    1140
gttctccctg acttggaaca tggcctgtcg gattatcctg cccccagaga aggagcttgc    1200
catgcccggg gaggacctga agttcaacct aatcttgcgg cagccaatga tcttagagaa    1260
aggccagcgt ttcaccctgc gagatggcaa ccggactatt ggcaccggtc tagtcaccaa    1320
cacgctggcc atgactgagg aggagaagaa tatcaaatgg ggttgagtgt gcagatctct    1380
gctcagcttc ccttgcgttt aaggcctgcc ctagccaggg ctccctcctg cttccagtac    1440
cctctcatgg cataggctgc aacccagcag agggcagcta gatggacatt tcccctgctc    1500
ggaagggttg gcctgcctgg ctggggaggt cagtaaactt tgaatagtaa gcca          1554
```

<210> 24
<211> 452
<212> PRT
<213> Homo sapiens

<400> 24

```
Met Ala Ala Ala Thr Leu Leu Arg Ala Thr Pro His Phe Ser Gly Leu
1               5                   10                  15
Ala Ala Gly Arg Thr Phe Leu Leu Gln Gly Leu Leu Arg Leu Leu Lys
            20                  25                  30
Ala Pro Ala Leu Pro Leu Leu Cys Arg Gly Leu Ala Val Glu Ala Lys
        35                  40                  45
Lys Thr Tyr Val Arg Asp Lys Pro His Val Asn Val Gly Thr Ile Gly
    50                  55                  60
His Val Asp His Gly Lys Thr Thr Leu Thr Ala Ala Ile Thr Lys Ile
65                  70                  75                  80
Leu Ala Glu Gly Gly Gly Ala Lys Phe Lys Lys Tyr Glu Glu Ile Asp
                85                  90                  95
Asn Ala Pro Glu Glu Arg Ala Arg Gly Ile Thr Ile Asn Ala Ala His
            100                 105                 110
Val Glu Tyr Ser Thr Ala Ala Arg His Tyr Ala His Thr Asp Cys Pro
        115                 120                 125
Gly His Ala Asp Tyr Val Lys Asn Met Ile Thr Gly Thr Ala Pro Leu
    130                 135                 140
Asp Gly Cys Ile Leu Val Val Ala Ala Asn Asp Gly Pro Met Pro Gln
145                 150                 155                 160
Thr Arg Glu His Leu Leu Leu Ala Arg Gln Ile Gly Val Glu His Val
                165                 170                 175
Val Val Tyr Val Asn Lys Ala Asp Ala Val Gln Asp Ser Glu Met Val
            180                 185                 190
Glu Leu Val Glu Leu Glu Ile Arg Glu Leu Leu Thr Glu Phe Gly Tyr
        195                 200                 205
Lys Gly Glu Glu Thr Pro Val Ile Val Gly Ser Ala Leu Cys Ala Leu
    210                 215                 220
Glu Gly Arg Asp Pro Glu Leu Gly Leu Lys Ser Val Gln Lys Leu Leu
225                 230                 235                 240
Asp Ala Val Asp Thr Tyr Ile Pro Val Pro Ala Arg Asp Leu Glu Lys
                245                 250                 255
Pro Phe Leu Leu Pro Val Glu Ala Val Tyr Ser Val Pro Gly Arg Gly
            260                 265                 270
```

```
Thr Val Val Thr Gly Thr Leu Glu Arg Gly Ile Leu Lys Lys Gly Asp
        275                 280                 285
Glu Cys Glu Leu Leu Gly His Ser Lys Asn Ile Arg Thr Val Val Thr
    290                 295                 300
Gly Ile Glu Met Phe His Lys Ser Leu Glu Arg Ala Glu Ala Gly Asp
305                 310                 315                 320
Asn Leu Gly Ala Leu Val Arg Gly Leu Lys Arg Glu Asp Leu Arg Arg
                325                 330                 335
Gly Leu Val Met Val Lys Pro Gly Ser Ile Lys Pro His Gln Lys Val
            340                 345                 350
Glu Ala Gln Val Tyr Ile Leu Ser Lys Glu Glu Gly Gly Arg His Lys
        355                 360                 365
Pro Phe Val Ser His Phe Met Pro Val Met Phe Ser Leu Thr Trp Asn
    370                 375                 380
Met Ala Cys Arg Ile Ile Leu Pro Pro Glu Lys Glu Leu Ala Met Pro
385                 390                 395                 400
Gly Glu Asp Leu Lys Phe Asn Leu Ile Leu Arg Gln Pro Met Ile Leu
                405                 410                 415
Glu Lys Gly Gln Arg Phe Thr Leu Arg Asp Gly Asn Arg Thr Ile Gly
            420                 425                 430
Thr Gly Leu Val Thr Asn Thr Leu Ala Met Thr Glu Glu Glu Lys Asn
        435                 440                 445
Ile Lys Trp Gly
    450
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<210> 25
<211> 2201
<212> DNA
<213> Homo sapiens

<400> 25

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tttttttttt cgtcttagcc acgcagaagt cgcgtgtcta gtttgtttcg acgccggacc      60
gcgtaagaga cgatgatgtt gggcacggaa ggtggagagg gattcgtggt gaaggtccgg     120
ggcttgccct ggtcttgctc ggccgatgaa gtgcagaggt ttttttctga ctgcaaaatt     180
caaaatgggg ctcaaggtat tcgtttcatc tacaccagag aaggcagacc aagtggcgag     240
gcttttgttg aacttgaatc agaagatgaa gtcaaattgg ccctgaaaaa agacagagaa     300
actatgggac acagatatgt tgaagtattc aagtcaaaca acgttgaaat ggattgggtg     360
ttgaagcata ctggtccaaa tagtcctgac acggccaatg atggctttgt acggcttaga     420
ggacttccct ttggatgtag caaggaagaa attgttcagt tcttctcagg gttggaaatc     480
gtgccaaatg ggataacatt gccggtggac ttccagggga ggagtacggg ggaggccttc     540
gtgcagtttg cttcacagga aatagctgaa aaggctctaa agaaacacaa ggaaagaata     600
gggcacaggt atattgaaat ctttaagagc agtagagctg aagttagaac tcattatgat     660
ccaccacgaa agcttatggc catgcagcgg ccaggtcctt atgacagacc tggggctggt     720
agagggtata acagcattgg cagaggagct ggctttgaga ggatgaggcg tggtgcttat     780
ggtggaggct atggaggcta tgatgattac aatggctata atgatggcta tggatttggg     840
tcagatagat ttggaagaga cctcaattac tgtttttcag gaatgtctga tcacagatac     900
ggggatggtg gctctacttt ccagagcaca acaggacact gtgtacacat gcggggatta     960
ccttacagag ctactgagaa tgacatttat aatttttttt caccgctcaa ccctgtgaga    1020
gtacacattg aaattggtcc tgatggcaga gtaactggtg aagcagatgt cgagttcgca    1080
actcatgaag atgctgtggc agctatgtca aaagacaaag caaatatgca acacagatat    1140
gtagaactct tcttgaattc tacagcagga gcaagcggtg gtgcttacga acacagatat    1200
gtagaactct tcttgaattc tacagcagga gcaagcggtg gtgcttatgg tagccaaatg    1260
atgggaggca tgggcttgtc aaaccagtcc agctacgggg gcccagccag ccagcagctg    1320
agtggggggtt acggaggcgg ctacggtggc cagagcagca tgagtggata cgaccaagtt    1380
ttacaggaaa actccagtga ttttcaatca aacattgcat aggtaaccaa ggagcagtga    1440
acagcagcta ctacagtagt ggaagccgtg catctatggg cgtgaacgga atgggagggt    1500
tgtctagcat gtccagtatg agtggtggat ggggaatgta attgatcgat cctgatcact    1560
gactcttggt caaccttttt tttttttttt ttttctttaa gaaaacttca gtttaacagt    1620
ttctgcaata caagcttgtg atttatgctt actctaagtg gaaatcagga ttgttatgaa    1680
gacttaaggc ccagtatttt tgaatacaat actcatctag gatgtaacag tgaagctgag    1740
```

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taaactataa ctgttaaact taagttccag cttttctcaa gttagttata ggatgtactt    1800
aagcagtaag cgtatttagg taaaagcagt tgaattatgt taaatgttgc cctttgccac    1860
gttaaattga acactgtttt ggatgcatgt tgaaagacat gcttttattt tttttgtaaa    1920
acaatatagg agctgtgtct actattaaaa gtgaaacatt ttggcatgtt tgttaattct    1980
agtttcattt aataacctgt aaggcacgta agtttaagct tttttttttt ttaagttaat    2040
gggaaaaatt tgagacgcaa taccaatact taggattttg gtcttggtgt ttgtatgaaa    2100
ttctgaggcc ttgatttaaa tctttcattg tattgtgatt tcctttttagg tatattgcgc   2160
taagtgaaac ttgtcaaata aatcctcctt ttaaaaactg c                        2201
```

<210> 26
<211> 449
<212> PRT
<213> Homo sapiens

<400> 26

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Met Met Leu Gly Thr Glu Gly Gly Glu Gly Phe Val Val Lys Val Arg
1               5                   10                  15
Gly Leu Pro Trp Ser Cys Ser Ala Asp Glu Val Gln Arg Phe Phe Ser
            20                  25                  30
Asp Cys Lys Ile Gln Asn Gly Ala Gln Gly Ile Arg Phe Ile Tyr Thr
        35                  40                  45
Arg Glu Gly Arg Pro Ser Gly Glu Ala Phe Val Glu Leu Glu Ser Glu
    50                  55                  60
Asp Glu Val Lys Leu Ala Leu Lys Lys Asp Arg Glu Thr Met Gly His
65                  70                  75                  80
Arg Tyr Val Glu Val Phe Lys Ser Asn Asn Val Glu Met Asp Trp Val
                85                  90                  95
Leu Lys His Thr Gly Pro Asn Ser Pro Asp Thr Ala Asn Asp Gly Phe
            100                 105                 110
Val Arg Leu Arg Gly Leu Pro Phe Gly Cys Ser Lys Glu Glu Ile Val
        115                 120                 125
Gln Phe Phe Ser Gly Leu Glu Ile Val Pro Asn Gly Ile Thr Leu Pro
    130                 135                 140
Val Asp Phe Gln Gly Arg Ser Thr Gly Glu Ala Phe Val Gln Phe Ala
145                 150                 155                 160
Ser Gln Glu Ile Ala Glu Lys Ala Leu Lys Lys His Lys Glu Arg Ile
                165                 170                 175
Gly His Arg Tyr Ile Glu Ile Phe Lys Ser Ser Arg Ala Glu Val Arg
            180                 185                 190
Thr His Tyr Asp Pro Pro Arg Lys Leu Met Ala Met Gln Arg Pro Gly
        195                 200                 205
Pro Tyr Asp Arg Pro Gly Ala Gly Arg Gly Tyr Asn Ser Ile Gly Arg
    210                 215                 220
Gly Ala Gly Phe Glu Arg Met Arg Arg Gly Ala Tyr Gly Gly Gly Tyr
225                 230                 235                 240
Gly Gly Tyr Asp Asp Tyr Asn Gly Tyr Asn Asp Gly Tyr Gly Phe Gly
                245                 250                 255
Ser Asp Arg Phe Gly Arg Asp Leu Asn Tyr Cys Phe Ser Gly Met Ser
            260                 265                 270
Asp His Arg Tyr Gly Asp Gly Gly Ser Thr Phe Gln Ser Thr Thr Gly
        275                 280                 285
His Cys Val His Met Arg Gly Leu Pro Tyr Arg Ala Thr Glu Asn Asp
    290                 295                 300
Ile Tyr Asn Phe Phe Ser Pro Leu Asn Pro Val Arg Val His Ile Glu
305                 310                 315                 320
Ile Gly Pro Asp Gly Arg Val Thr Gly Glu Ala Asp Val Glu Phe Ala
                325                 330                 335
Thr His Glu Asp Ala Val Ala Ala Met Ser Lys Asp Lys Ala Asn Met
            340                 345                 350
```

Gln His Arg Tyr Val Glu Leu Phe Leu Asn Ser Thr Ala Gly Ala Ser
355 360 365
Gly Gly Ala Tyr Glu His Arg Tyr Val Glu Leu Phe Leu Asn Ser Thr
370 375 380
Ala Gly Ala Ser Gly Gly Ala Tyr Gly Ser Gln Met Met Gly Gly Met
385 390 395 400
Gly Leu Ser Asn Gln Ser Ser Tyr Gly Gly Pro Ala Ser Gln Gln Leu
405 410 415
Ser Gly Gly Tyr Gly Gly Gly Tyr Gly Gly Gln Ser Ser Met Ser Gly
420 425 430
Tyr Asp Gln Val Leu Gln Glu Asn Ser Ser Asp Phe Gln Ser Asn Ile
435 440 445
Ala

<210> 27
<211> 1852
<212> DNA
<213> Homo sapiens

<400> 27
acagcccttc gtggggccct gggcaccctg caccagctgg gcatcgtcgt cggcatcctc 60
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ctgagcatca tcttcatccc ggccctgctg cagtgcatcg tgctgccctt ctgccccgag 180
agtccccgct tcctgctcat caaccgcaac gaggagaacc gggccaagag tgtgctaaag 240
aagctgcgcg ggacagctga cgtgacccat gacctgcagg agatgaagga agagagtcgg 300
cagatgatgc gggagaagaa ggtcaccatc ctggagctgt tccgctcccc cgcctaccgc 360
cagcccatcc tcatcgctgt ggtgctgcag ctgtcccagc agctgtctgg catcaacgct 420
gtcttctatt actccacgag catcttcgag aaggcggggg tgcagcagcc tgtgtatgcc 480
accattggct ccggtatcgt caacacggcc ttcactgtcg tgtcgctgtt tgtggtggag 540
cgagcaggcc ggcggaccct gcacctcata ggcctcgctg gcatggcggg ttgtgccata 600
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gtggccatct ttggctttgt ggccttcttt gaagtgggtc ctggccccat cccatggttc 720
atcgtggctg aactcttcag ccagggtcca cgtccagctg ccattgccgt tgcaggcttc 780
tccaactgga cctcaaattt cattgtgggc atgtgcttcc agtatgtgga gcaactgtgt 840
ggtccctacg tcttcatcat cttcactgtg ctcctggttc tgttcttcat cttcacctac 900
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ctccaggatt ttaacaaaag caagactgtt gctcaaatct attcagacaa gcaacaggtt 1260
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ttgtcaatat taaatacaga cactaagtta tagtaaaaaa aaaaaaaaaa aa 1852

<210> 28
<211> 343
<212> PRT
<213> Homo sapiens

<400> 28

Thr Ala Leu Arg Gly Ala Leu Gly Thr Leu His Gln Leu Gly Ile Val
1 5 10 15
Val Gly Ile Leu Ile Ala Gln Val Phe Gly Leu Asp Ser Ile Met Gly
20 25 30
Asn Lys Asp Leu Trp Pro Leu Leu Leu Ser Ile Ile Phe Ile Pro Ala
35 40 45
Leu Leu Gln Cys Ile Val Leu Pro Phe Cys Pro Glu Ser Pro Arg Phe
50 55 60
Leu Leu Ile Asn Arg Asn Glu Glu Asn Arg Ala Lys Ser Val Leu Lys
65 70 75 80
Lys Leu Arg Gly Thr Ala Asp Val Thr His Asp Leu Gln Glu Met Lys
85 90 95
Glu Glu Ser Arg Gln Met Met Arg Glu Lys Lys Val Thr Ile Leu Glu
100 105 110
Leu Phe Arg Ser Pro Ala Tyr Arg Gln Pro Ile Leu Ile Ala Val Val
115 120 125
Leu Gln Leu Ser Gln Gln Leu Ser Gly Ile Asn Ala Val Phe Tyr Tyr
130 135 140
Ser Thr Ser Ile Phe Glu Lys Ala Gly Val Gln Gln Pro Val Tyr Ala
145 150 155 160
Thr Ile Gly Ser Gly Ile Val Asn Thr Ala Phe Thr Val Val Ser Leu
165 170 175
Phe Val Val Glu Arg Ala Gly Arg Arg Thr Leu His Leu Ile Gly Leu
180 185 190
Ala Gly Met Ala Gly Cys Ala Ile Leu Met Thr Ile Ala Leu Ala Leu
195 200 205
Leu Glu Gln Leu Pro Trp Met Ser Tyr Leu Ser Ile Val Ala Ile Phe
210 215 220
Gly Phe Val Ala Phe Phe Glu Val Gly Pro Gly Pro Ile Pro Trp Phe
225 230 235 240
Ile Val Ala Glu Leu Phe Ser Gln Gly Pro Arg Pro Ala Ala Ile Ala
245 250 255
Val Ala Gly Phe Ser Asn Trp Thr Ser Asn Phe Ile Val Gly Met Cys
260 265 270
Phe Gln Tyr Val Glu Gln Leu Cys Gly Pro Tyr Val Phe Ile Ile Phe
275 280 285
Thr Val Leu Leu Val Leu Phe Phe Ile Phe Thr Tyr Phe Lys Val Pro
290 295 300
Glu Thr Lys Gly Arg Thr Phe Asp Glu Ile Ala Ser Gly Phe Arg Gln
305 310 315 320
Gly Gly Ala Ser Gln Ser Asp Lys Thr Pro Glu Glu Leu Phe His Pro
325 330 335
Leu Gly Ala Asp Ser Gln Val
340

<210> 29
<211> 5368
<212> DNA
<213> Homo sapiens

<400> 29
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agatggagga accctagggg ttttctcacc taaaaagacc ccacatcttg ttaacctcaa 180
tgaagaccca ctaatgtctg agtgcctact ttattacatc aaagatggaa ttacaagggt 240
tggccaagca gatgctgagc ggcgccagga catagtgctg agcggggctc acattaaaga 300
agagcattgt atcttccgga gtgagagaag caacagcggg gaagttatcg tgaccttaga 360
gccctgtgag cgctcagaaa cctacgtaaa tggcaagagg gtgtcccagc ctgttcagct 420
gcgctcagga aaccgtatca tcatgggtaa aaaccatgtt ttccgcttta accacccgga 480
acaagcacga gctgagcgag agaagactcc ttctgctgag accccctctg agcctgtgga 540

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ctggacattt gcccagaggg agcttctgga aaaacaagga attgatatga aacaagagat    600
ggagaaaagg ctacaggaaa tggagatctt atacaaaaag gagaaggaag aagcagatct    660
tcttttggag cagcagagac tggactatga gagtaaattg caggccttgc agaagcaggt    720
tgaaacccga tctctggctg cagaaacaac tgaagaggag gaagaagagg aagaagttcc    780
ttggacacag catgaatttg agttggccca atgggccttc cggaaatgga agtctcatca    840
gtttacttca ttacgggact tactctgggg caatgccgtg tacctaaagg aggccaatgc    900
catcagtgtg gaactgaaaa agaaggtgca gtttcagttt gttctgctga ctgacacact    960
gtactcccct ttgcctcctg aattacttcc cactgagatg gaaaaaactc atgaggacag   1020
gcctttccct cgcacagtgg tagcagtaga agtccaggat ttgaagaatg gagcaacaca   1080
ctattggtct ttggagaaac tcaagcagag gctggatttg atgcgagaga tgtatgatag   1140
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tcccttctat gatcggttcc actggttcaa acttgtgggg agctccccca ttttccacgg   1260
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cgacatcact gagctggctg acgagcagca agatgagatg gaggattttg atgatgaggc   1380
attcgtggat gacgccggct ctgacgcagg gacggaggag ggatcagatc tcttcagtga   1440
cgggcatgac ccgttttacg accgatcccc ttggttcatt ttagtgggaa gggcatttgt   1500
ttacctgagc aatctgctgt atcccgtgcc cctgatccac agggtggcca tcgtcagtga   1560
gaaaggtgaa gtgcggggat ttctgcgtgt ggctgtacag gccatcgcag cggatgaaga   1620
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ggaggagttg aggattgtgg aaggacaggg tcagagttct gaggtcatca ctcctccaga   1800
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ggtaatggaa gggttttctg aagagattgg caaccacctg aaactgggca gtgccttcac   1920
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<213> Homo sapiens

<400> 30

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Glu Met Gly Val Ala Ile Arg Glu Asp Gly Gly Thr Leu Gly Val Phe
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Ser Pro Lys Lys Thr Pro His Leu Val Asn Leu Asn Glu Asp Pro Leu
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Met Ser Glu Cys Leu Leu Tyr Tyr Ile Lys Asp Gly Ile Thr Arg Val
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Gly Gln Ala Asp Ala Glu Arg Arg Gln Asp Ile Val Leu Ser Gly Ala
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His Ile Lys Glu Glu His Cys Ile Phe Arg Ser Glu Arg Ser Asn Ser
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Gly Glu Val Ile Val Thr Leu Glu Pro Cys Glu Arg Ser Glu Thr Tyr
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Val Asn Gly Lys Arg Val Ser Gln Pro Val Gln Leu Arg Ser Gly Asn
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Arg Ile Ile Met Gly Lys Asn His Val Phe Arg Phe Asn His Pro Glu
145                 150                 155                 160
Gln Ala Arg Ala Glu Arg Glu Lys Thr Pro Ser Ala Glu Thr Pro Ser
                165                 170                 175
Glu Pro Val Asp Trp Thr Phe Ala Gln Arg Glu Leu Leu Glu Lys Gln
            180                 185                 190
Gly Ile Asp Met Lys Gln Glu Met Glu Lys Arg Leu Gln Glu Met Glu
        195                 200                 205
Ile Leu Tyr Lys Lys Glu Lys Glu Glu Ala Asp Leu Leu Leu Glu Gln
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Gln Arg Leu Asp Tyr Glu Ser Lys Leu Gln Ala Leu Gln Lys Gln Val
225                 230                 235                 240
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Glu Glu Val Pro Trp Thr Gln His Glu Phe Glu Leu Ala Gln Trp Ala
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Trp Gly Asn Ala Val Tyr Leu Lys Glu Ala Asn Ala Ile Ser Val Glu
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Leu Lys Lys Lys Val Gln Phe Gln Phe Val Leu Leu Thr Asp Thr Leu
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Tyr Ser Pro Leu Pro Pro Glu Leu Leu Pro Thr Glu Met Glu Lys Thr
325 330 335
His Glu Asp Arg Pro Phe Pro Arg Thr Val Val Ala Val Glu Val Gln
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Asp Leu Lys Asn Gly Ala Thr His Tyr Trp Ser Leu Glu Lys Leu Lys
355 360 365
Gln Arg Leu Asp Leu Met Arg Glu Met Tyr Asp Arg Ala Gly Glu Met
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385 390 395 400
Pro Phe Tyr Asp Arg Phe His Trp Phe Lys Leu Val Gly Ser Ser Pro
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Ile Phe His Gly Cys Val Asn Glu Arg Leu Ala Asp Arg Thr Pro Ser
420 425 430
Pro Thr Phe Ser Thr Ala Asp Ser Asp Ile Thr Glu Leu Ala Asp Glu
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Gln Gln Asp Glu Met Glu Asp Phe Asp Asp Glu Ala Phe Val Asp Asp
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485 490 495
Arg Ala Phe Val Tyr Leu Ser Asn Leu Leu Tyr Pro Val Pro Leu Ile
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Gly Ser Gly Ile Arg Gln Ser Gly Thr Ala Lys Ile Ser Phe Asp Asn
545 550 555 560
Glu Tyr Phe Asn Gln Ser Asp Phe Ser Ser Val Ala Met Thr Arg Ser
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Gly Leu Ser Leu Glu Glu Leu Arg Ile Val Glu Gly Gln Gly Gln Ser
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Ser Glu Val Ile Thr Pro Pro Glu Glu Ile Ser Arg Ile Asn Asp Leu
595 600 605
Asp Leu Lys Ser Ser Thr Leu Leu Asp Gly Lys Met Val Met Glu Gly
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Phe Ser Glu Glu Ile Gly Asn His Leu Lys Leu Gly Ser Ala Phe Thr
625 630 635 640
Phe Arg Val Thr Val Leu Gln Ala Ser Gly Ile Leu Pro Glu Tyr Ala
645 650 655
Asp Ile Phe Cys Gln Phe Asn Phe Leu His Arg His Asp Glu Ala Phe
660 665 670
Ser Thr Glu Pro Leu Lys Asn Asn Gly Arg Gly Ser Pro Leu Ala Phe
675 680 685
Tyr His Val Gln Asn Ile Ala Val Glu Ile Thr Glu Ser Phe Val Asp
690 695 700
Tyr Ile Lys Thr Lys Pro Ile Val Phe Glu Val Phe Gly His Tyr Gln
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Pro Ala Thr Lys Leu Asn Thr Met Ser Lys Thr Ser Leu Gly Gln Ser
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Met Ser Lys Tyr Asp Leu Leu Val Trp Phe Glu Ile Ser Glu Leu Glu
    770                 775                 780
Pro Thr Gly Glu Tyr Ile Pro Ala Val Val Asp His Thr Ala Gly Leu
785                 790                 795                 800
Pro Cys Gln Gly Thr Phe Leu Leu His Gln Gly Ile Gln Arg Arg Ile
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Thr Val Thr Ile Ile His Glu Lys Gly Ser Glu Leu His Trp Lys Asp
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Val Arg Glu Leu Val Val Gly Arg Ile Arg Asn Lys Pro Glu Val Asp
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Tyr Leu Lys Ser Ser His Asn Ser Ser Arg Thr Phe Tyr Arg Phe Glu
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Ala Val Trp Asp Ser Ser Leu His Asn Ser Leu Leu Leu Asn Arg Val
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Thr Pro Tyr Gly Glu Lys Ile Tyr Met Thr Leu Ser Ala Tyr Leu Glu
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Leu Asp His Cys Ile Gln Pro Ala Val Ile Thr Lys Asp Val Cys Met
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Val Phe Tyr Ser Arg Asp Ala Lys Ile Ser Pro Pro Arg Ser Leu Arg
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Pro Gly Met Gln Arg Arg Arg Arg Lys Ile Leu Asp Thr Ser Val Ala
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Ser Leu Ile Leu Glu His Gln Trp Glu Leu Glu Lys Leu Glu Leu Leu
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Ile Gly Arg Asp Pro Ser Glu Ser Ser Phe Ser Ser Ala Thr Leu Thr
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Pro Ser Ser Thr Cys Pro Ser Leu Val Asp Ser Arg Ser Asn Ser Leu
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Asp Gln Lys Thr Pro Glu Ala Asn Ser Arg Ala Ser Ser Pro Cys Pro
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Glu Phe Glu Gln Phe Gln Ile Val Pro Ala Val Glu Thr Pro Tyr Leu
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Lys Glu Pro Leu Tyr Ser Asn Trp Ala Lys His Phe Val Val Val Arg
1235 1240 1245
Arg Pro Tyr Val Phe Ile Tyr Asn Ser Asp Lys Asp Pro Val Glu Arg
1250 1255 1260
Gly Ile Ile Asn Leu Ser Thr Ala Gln Val Glu Tyr Ser Glu Asp Gln
1265 1270 1275 1280
Gln Ala Met Val Lys Thr Pro Asn Thr Phe Ala Val Cys Thr Lys His
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Arg Gly Val Leu Leu Gln Ala Leu Asn Asp Lys Asp Met Asn Asp Trp
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<212> PRT
<213> Homo sapiens

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35 40 45
Pro Glu Gly Thr Gly Lys Thr Glu Met Leu Tyr His Leu Thr Ala Arg
50 55 60
Cys Ile Leu Pro Lys Ser Glu Gly Gly Leu Glu Val Glu Val Leu Phe
65 70 75 80
Ile Asp Thr Asp Tyr His Phe Asp Met Leu Arg Leu Val Thr Ile Leu
85 90 95
Glu His Arg Leu Ser Gln Ser Ser Glu Glu Ile Ile Lys Tyr Cys Leu
100 105 110
Gly Arg Phe Phe Leu Val Tyr Cys Ser Ser Ser Thr His Leu Leu Leu
115 120 125
Thr Leu Tyr Ser Leu Glu Ser Met Phe Cys Ser His Pro Ser Leu Cys
130 135 140
Leu Leu Ile Leu Asp Ser Leu Ser Ala Phe Tyr Trp Ile Asp Arg Val
145 150 155 160
Asn Gly Gly Glu Ser Val Asn Leu Gln Glu Ser Thr Leu Arg Lys Cys
165 170 175
Ser Gln Cys Leu Glu Lys Leu Val Asn Asp Tyr Arg Leu Val Leu Phe
180 185 190
Ala Thr Thr Gln Thr Ile Met Gln Lys Ala Ser Ser Ser Ser Glu Glu
195 200 205
Pro Ser His Ala Ser Arg Arg Leu Cys Asp Val Asp Ile Asp Tyr Arg
210 215 220
Pro Tyr Leu Cys Lys Ala Trp Gln Gln Leu Val Lys His Arg Met Phe
225 230 235 240
Phe Ser Lys Gln Asp Asp Ser Gln Ser Ser Asn Gln Phe Ser Leu Val
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<213> Homo sapiens

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Phe Phe Asn Gly Ala Asn Val Arg Gln Val Asp Val Pro Thr Leu Thr
50 55 60
Gly Ala Phe Gly Ile Leu Ala Ala His Val Pro Thr Leu Gln Val Leu
65 70 75 80
Arg Pro Gly Leu Val Val Val His Ala Glu Asp Gly Thr Thr Ser Lys
85 90 95
Tyr Phe Val Ser Ser Gly Ser Ile Ala Val Asn Ala Asp Ser Ser Val
100 105 110
Gln Leu Leu Ala Glu Glu Ala Val Thr Leu Asp Met Leu Asp Leu Gly
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Ala Ala Lys Ala Asn Leu Glu Lys Ala Gln Ala Glu Leu Val Gly Thr
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<210> 35
<211> 1378
<212> DNA
<213> Homo sapiens

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cgtggtggtc ttggaagagg tcgagggggc cgtggacgtg gaatgggccg aggagatgga 600
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gaatttaata tccgaaaacc aaatgaaggt gctgatgggc agtggaagaa gggatttgtt 1020
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<210> 36
<211> 2896
<212> DNA
<213> Homo sapiens

<400> 36

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atgtatttca gaaagg 2896

<210> 37
<211> 777
<212> PRT
<213> Homo sapiens

<400> 37
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Ser Gln Leu Leu Leu Glu Thr Asp Trp Glu Ser Ile Leu Gln Ile Cys
            20   25   30
Asp Leu Ile Arg Gln Gly Asp Thr Gln Ala Lys Tyr Ala Val Asn Ser
        35   40   45
Ile Lys Lys Lys Val Asn Asp Lys Asn Pro His Val Ala Leu Tyr Ala
    50   55   60
Leu Glu Val Met Glu Ser Val Val Lys Asn Cys Gly Gln Thr Val His
65   70   75   80
Asp Glu Val Ala Asn Lys Gln Thr Met Glu Glu Leu Lys Asp Leu Leu
                85   90   95
Lys Arg Gln Val Glu Val Asn Val Arg Asn Lys Ile Leu Tyr Leu Ile
            100   105   110
Gln Ala Trp Ala His Ala Phe Arg Asn Glu Pro Lys Tyr Lys Val Val
        115   120   125
Gln Asp Thr Tyr Gln Ile Met Lys Val Glu Gly His Val Phe Pro Glu
    130   135   140
Phe Lys Glu Ser Asp Ala Met Phe Ala Ala Glu Arg Ala Pro Asp Trp
145   150   155   160
Val Asp Ala Glu Glu Cys His Arg Cys Arg Val Gln Phe Gly Val Met
                165   170   175
Thr Arg Lys His His Cys Arg Ala Cys Gly Gln Ile Phe Cys Gly Lys
            180   185   190
Cys Ser Ser Lys Tyr Ser Thr Ile Pro Lys Phe Gly Ile Glu Lys Glu
        195   200   205
Val Arg Val Cys Glu Pro Cys Tyr Glu Gln Leu Asn Arg Lys Ala Glu
    210   215   220
Gly Lys Ala Thr Ser Thr Thr Glu Leu Pro Pro Glu Tyr Leu Thr Ser
225   230   235   240
Pro Leu Ser Gln Gln Ser Gln Leu Pro Pro Lys Arg Asp Glu Thr Ala
                245   250   255
Leu Gln Glu Glu Glu Glu Leu Gln Leu Ala Leu Ala Leu Ser Gln Ser
            260   265   270
Glu Ala Glu Glu Lys Glu Arg Leu Arg Gln Lys Ser Thr Tyr Thr Ser
        275   280   285
Tyr Pro Lys Ala Glu Pro Met Pro Ser Ala Ser Ser Ala Pro Pro Ala
    290   295   300
Ser Ser Leu Tyr Ser Ser Pro Val Asn Ser Ser Ala Pro Leu Ala Glu
305   310   315   320

Asp Ile Asp Pro Glu Leu Ala Arg Tyr Leu Asn Arg Asn Tyr Trp Glu
325 330 335
Lys Lys Gln Glu Glu Ala Arg Lys Ser Pro Thr Pro Ser Ala Pro Val
340 345 350
Pro Leu Thr Glu Pro Ala Ala Gln Pro Gly Glu Gly His Ala Ala Pro
355 360 365
Thr Asn Val Val Glu Asn Pro Leu Pro Glu Thr Asp Ser Gln Pro Ile
370 375 380
Pro Pro Ser Gly Gly Pro Phe Ser Glu Pro Gln Phe His Asn Gly Glu
385 390 395 400
Ser Glu Glu Ser His Glu Gln Phe Leu Lys Ala Leu Gln Asn Ala Val
405 410 415
Thr Thr Phe Val Asn Arg Met Lys Ser Asn His Met Arg Gly Arg Ser
420 425 430
Ile Thr Asn Asp Ser Ala Val Leu Ser Leu Phe Gln Ser Ile Asn Gly
435 440 445
Met His Pro Gln Leu Leu Glu Leu Leu Asn Gln Leu Asp Glu Arg Arg
450 455 460
Leu Tyr Tyr Glu Gly Leu Gln Asp Lys Leu Ala Gln Ile Arg Asp Ala
465 470 475 480
Arg Gly Ala Leu Ser Ala Leu Arg Glu Glu His Arg Glu Lys Leu Arg
485 490 495
Arg Ala Ala Glu Glu Ala Glu Arg Gln Arg Gln Ile Gln Leu Ala Gln
500 505 510
Lys Leu Glu Ile Met Arg Gln Lys Lys Gln Glu Tyr Leu Glu Val Gln
515 520 525
Arg Gln Leu Ala Ile Gln Arg Leu Gln Glu Gln Glu Lys Glu Arg Gln
530 535 540
Met Arg Leu Glu Gln Gln Lys Gln Thr Val Gln Met Arg Ala Gln Met
545 550 555 560
Pro Ala Phe Pro Leu Pro Tyr Ala Gln Leu Gln Ala Met Pro Ala Ala
565 570 575
Gly Gly Val Leu Tyr Gln Pro Ser Gly Pro Ala Ser Phe Pro Ser Thr
580 585 590
Phe Ser Pro Ala Gly Ser Val Glu Gly Ser Pro Met His Gly Val Tyr
595 600 605
Met Ser Gln Pro Ala Pro Ala Ala Gly Pro Tyr Pro Ser Met Pro Ser
610 615 620
Thr Ala Ala Asp Pro Ser Met Val Ser Ala Tyr Met Tyr Pro Ala Gly
625 630 635 640
Ala Thr Gly Ala Gln Ala Ala Pro Gln Ala Gln Ala Gly Pro Thr Ala
645 650 655
Ser Pro Ala Tyr Ser Ser Tyr Gln Pro Thr Pro Thr Ala Gly Tyr Gln
660 665 670
Asn Val Ala Ser Gln Ala Pro Gln Ser Leu Pro Ala Ile Ser Gln Pro
675 680 685
Pro Gln Ser Ser Thr Met Gly Tyr Met Gly Ser Gln Ser Val Ser Met
690 695 700
Gly Tyr Gln Pro Tyr Asn Met Gln Asn Leu Met Thr Thr Leu Pro Ser
705 710 715 720
Gln Asp Ala Ser Leu Pro Pro Gln Gln Pro Tyr Ile Ala Gly Gln Gln
725 730 735
Pro Met Tyr Gln Gln Met Ala Pro Ser Gly Gly Pro Pro Gln Gln Gln
740 745 750
Pro Pro Val Ala Gln Gln Pro Gln Ala Gln Gly Pro Pro Ala Gln Gly
755 760 765
Ser Glu Ala Gln Leu Ile Ser Phe Asp
770 775

<210> 38

<211> 2569
<212> DNA
<213> Homo sapiens

<400> 38
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agcagccaag aaaaaaagac gaaagaagaa gaagagcaaa gggccttctg cagcagggga 180
acaggaacct gataaagaat caggagcctc agtggatgaa gtagcaagac agttggaaag 240
atcagcattg gaagataaag aaagagatga agatgatgaa gatggagatg gcgatggaga 300
tggagcaact ggaaagaaga agaaaaagaa gaagaagaag agaggaccaa aagttcaaac 360
agaccctccc tcagttccaa tatgtgacct gtatcctaat ggtgtatttc ccaaaggaca 420
agaatgcgaa tacccaccca cacaagatgg gcgaacagct gcttggagaa ctacaagtga 480
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agaagcacat cgacaagtta gaaaatacgt aatgagctgg atcaagcctg ggatgacaat 600
gatagaaatc tgtgaaaagt tggaagactg ttcacgcaag ttaataaaag agaatggatt 660
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gaatgactac atccagttct gcacctatac cctctggtgt tgcttttttaa ccttcctgga 1860
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gcccacaaga gaaagcagga aatatctaaa attgacaccc taacatcaca attaaaagaa 2280
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<210> 39
<211> 478
<212> PRT
<213> Homo sapiens

<400> 39
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Asp Leu Asp Pro Asp Asp Arg Glu Glu Gly Ala Ala Ser Thr Ala Glu
20 25 30

Glu Ala Ala Lys Lys Lys Arg Arg Lys Lys Lys Lys Ser Lys Gly Pro
        35   40   45
Ser Ala Ala Gly Glu Gln Glu Pro Asp Lys Glu Ser Gly Ala Ser Val
    50   55   60
Asp Glu Val Ala Arg Gln Leu Glu Arg Ser Ala Leu Glu Asp Lys Glu
65   70   75   80
Arg Asp Glu Asp Asp Glu Asp Gly Asp Gly Asp Gly Asp Gly Ala Thr
                85   90   95
Gly Lys Lys Lys Lys Lys Lys Lys Lys Lys Arg Gly Pro Lys Val Gln
            100   105   110
Thr Asp Pro Pro Ser Val Pro Ile Cys Asp Leu Tyr Pro Asn Gly Val
        115   120   125
Phe Pro Lys Gly Gln Glu Cys Glu Tyr Pro Pro Thr Gln Asp Gly Arg
    130   135   140
Thr Ala Ala Trp Arg Thr Thr Ser Glu Glu Lys Lys Ala Leu Asp Gln
145   150   155   160
Ala Ser Glu Glu Ile Trp Asn Asp Phe Arg Glu Ala Ala Glu Ala His
                165   170   175
Arg Gln Val Arg Lys Tyr Val Met Ser Trp Ile Lys Pro Gly Met Thr
            180   185   190
Met Ile Glu Ile Cys Glu Lys Leu Glu Asp Cys Ser Arg Lys Leu Ile
        195   200   205
Lys Glu Asn Gly Leu Asn Ala Gly Leu Ala Phe Pro Thr Gly Cys Ser
    210   215   220
Leu Asn Asn Cys Ala Ala His Tyr Thr Pro Asn Ala Gly Asp Thr Thr
225   230   235   240
Val Leu Gln Tyr Asp Asp Ile Cys Lys Ile Asp Phe Gly Thr His Ile
                245   250   255
Ser Gly Arg Ile Ile Asp Cys Ala Phe Thr Val Thr Phe Asn Pro Lys
            260   265   270
Tyr Asp Thr Leu Leu Lys Ala Val Lys Asp Ala Thr Asn Thr Gly Ile
        275   280   285
Lys Cys Ala Gly Ile Asp Val Arg Leu Cys Asp Val Gly Glu Ala Ile
    290   295   300
Gln Glu Val Met Glu Ser Tyr Glu Val Glu Ile Asp Gly Lys Thr Tyr
305   310   315   320
Gln Val Lys Pro Ile Arg Asn Leu Asn Gly His Ser Ile Gly Gln Tyr
                325   330   335
Arg Ile His Ala Gly Lys Thr Val Pro Ile Val Lys Gly Gly Glu Ala
            340   345   350
Thr Arg Met Glu Glu Gly Glu Val Tyr Ala Ile Glu Thr Phe Gly Ser
        355   360   365
Thr Gly Lys Gly Val Val His Asp Asp Met Glu Cys Ser His Tyr Met
    370   375   380
Lys Asn Phe Asp Val Gly His Val Pro Ile Arg Leu Pro Arg Thr Lys
385   390   395   400
His Leu Leu Asn Val Ile Asn Glu Asn Phe Gly Thr Leu Ala Phe Cys
                405   410   415
Arg Arg Trp Leu Asp Arg Leu Gly Glu Ser Lys Tyr Leu Met Ala Leu
            420   425   430
Lys Asn Leu Cys Asp Leu Gly Ile Val Asp Pro Tyr Pro Pro Leu Cys
        435   440   445
Asp Ile Lys Gly Ser Tyr Thr Ala Gln Phe Glu His Thr Ile Leu Leu
    450   455   460
Arg Pro Thr Cys Lys Glu Val Val Ser Arg Gly Asp Asp Tyr
465   470   475

<210> 40
<211> 1183
<212> DNA

<213> Homo sapiens

<220>
<221> misc_feature
<222> (0)...(0)
<223> n = a, t, c or g

<400> 40
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agttctatct gaatcctgac caatcaggcg agtttatgtt tgactttgat ggtgatgaga     180
ttttccatgt ggatatggca aagaaggaga cggtctggcg gcttgaagaa tttggacgat     240
ttgccagctt tgaggctcaa ggtgcattgg ccaacatagc tgtggacaaa gccaacttgg     300
aaatcatgac aaagcgctcc aactatactc cgatcaccaa tgtacctcca gaggtaactg     360
tgctcacgaa cagccctgtg gaactgagag agcccaacgt cctcatctgt ttcatcgaca     420
agttcacccc accagtggtc aatgtcacgt ggcttcgaaa tggaaaacct gtcaccacag     480
gagtgtcaga gacagtcttc ctgcccaggg aagaccacct tttccgcaag ttccactatc     540
tcccctttcct gccctcaact gaggacgttt acgactgcag ggtggagcac tggggcttgg     600
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agaacgtggt gtgtgccctg ggcctgactg tgggtctggt gggcatcatt attgggacca     720
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gcacatggag gtgatgatgt ttcttagaga gaagatcact gaagaaactt ctgctttaat     840
gactttacaa agctggcaat attacaatcc ttgacctcag tgaaagcagt catcttcagc     900
gttttccagc cctatagcca ccccaagtgt ggttatgcct cctcgattgc tccgtactct     960
aacatctagc tggcttccct gtctattgcc ttttcctgta tctattttcc tctatttcct    1020
atcattttat tatcaccatg caatgcctct ggaataaaac atacaggagt ctgtctctgc    1080
tatggaatgc cccatggggc atctcttgtg tacttattgt ttaaggtttc ctcaaactgn    1140
gattcttctg aacacaataa actattttga tgatcttggg tgg                      1183
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<210> 41
<211> 254
<212> PRT
<213> Homo sapiens

<400> 41
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Met Ala Ile Ser Gly Val Pro Val Leu Gly Phe Phe Ile Ile Ala Val
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Leu Met Ser Ala Gln Glu Ser Trp Ala Ile Lys Glu Glu His Val Ile
            20                  25                  30
Ile Gln Ala Glu Phe Tyr Leu Asn Pro Asp Gln Ser Gly Glu Phe Met
        35                  40                  45
Phe Asp Phe Asp Gly Asp Glu Ile Phe His Val Asp Met Ala Lys Lys
    50                  55                  60
Glu Thr Val Trp Arg Leu Glu Glu Phe Gly Arg Phe Ala Ser Phe Glu
65                  70                  75                  80
Ala Gln Gly Ala Leu Ala Asn Ile Ala Val Asp Lys Ala Asn Leu Glu
                85                  90                  95
Ile Met Thr Lys Arg Ser Asn Tyr Thr Pro Ile Thr Asn Val Pro Pro
            100                 105                 110
Glu Val Thr Val Leu Thr Asn Ser Pro Val Glu Leu Arg Glu Pro Asn
        115                 120                 125
Val Leu Ile Cys Phe Ile Asp Lys Phe Thr Pro Pro Val Val Asn Val
    130                 135                 140
Thr Trp Leu Arg Asn Gly Lys Pro Val Thr Thr Gly Val Ser Glu Thr
145                 150                 155                 160
Val Phe Leu Pro Arg Glu Asp His Leu Phe Arg Lys Phe His Tyr Leu
                165                 170                 175
Pro Phe Leu Pro Ser Thr Glu Asp Val Tyr Asp Cys Arg Val Glu His
            180                 185                 190
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```
Trp Gly Leu Asp Glu Pro Leu Leu Lys His Trp Glu Phe Asp Ala Pro
        195                 200                 205
Ser Pro Leu Pro Glu Thr Thr Glu Asn Val Val Cys Ala Leu Gly Leu
    210                 215                 220
Thr Val Gly Leu Val Gly Ile Ile Ile Gly Thr Ile Phe Ile Ile Lys
225                 230                 235                 240
Gly Val Arg Lys Ser Asn Ala Ala Glu Arg Arg Gly Pro Leu
                245                 250
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<210> 42
<211> 266
<212> DNA
<213> Homo sapiens

<400> 42
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ggcaaggact ggcatcggcc ctgcctgaag tgcgagaaat gtgggaagac gctgacctct     120
gggggccacg ctgagcacga aggcaaaccc tactgcaacc acccctgcta cgcagccatg     180
tttgggccta aaggctttgg gcggggcgga gccgagagcc acactttcaa gtaaaccagg     240
tggtggagac ccatccttgg ctgctt                                          266
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<210> 43
<211> 77
<212> PRT
<213> Homo sapiens

<400> 43
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Met Pro Lys Cys Pro Lys Cys Asn Lys Glu Val Tyr Phe Ala Glu Arg
 1               5                  10                  15
Val Thr Ser Leu Gly Lys Asp Trp His Arg Pro Cys Leu Lys Cys Glu
            20                  25                  30
Lys Cys Gly Lys Thr Leu Thr Ser Gly Gly His Ala Glu His Glu Gly
        35                  40                  45
Lys Pro Tyr Cys Asn His Pro Cys Tyr Ala Ala Met Phe Gly Pro Lys
    50                  55                  60
Gly Phe Gly Arg Gly Gly Ala Glu Ser His Thr Phe Lys
65                  70                  75
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<210> 44
<211> 1665
<212> DNA
<213> Homo sapiens

<400> 44
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actcacggtg caaaggtgca ctctgcgaac gttaagtccg tccccagcgc ttggaatcct     120
acggccccca cagccggatc ccctcagcct tccaggtcct caactcccgt ggacgctgaa     180
caatggcctc catggggcta caggtaatgg gcatcgcgct ggccgtcctg ggctggctgg     240
ccgtcatgct gtgctgcgcg ctgcccatgt ggcgcgtgac ggccttcatc ggcagcaaca     300
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cccgctctgc tgctgccagc aactacgtgt aaggtgccac ggctccactc tgttcctctc     840
tgctttgttc ttccctggac tgagctcagc gcaggctgtg accccaggag ggccctgcca     900
cgggccactg gctgctgggg actggggact gggcagagac tgagccaggc aggaaggcag     960
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gagtggggag ctggcttctg ctggccagga tagcttaacc ctgactttgg gatctgcctg 1140
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gtttttcctc ttccttcttt gtggtttctg ttttgtaatt taagaagagc tattcatcac 1620
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<210> 45
<211> 209
<212> PRT
<213> Homo sapiens

<400> 45
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35 40 45
Gly Leu Trp Met Asn Cys Val Val Gln Ser Thr Gly Gln Met Gln Cys
50 55 60
Lys Val Tyr Asp Ser Leu Leu Ala Leu Pro Gln Asp Leu Gln Ala Ala
65 70 75 80
Arg Ala Leu Val Ile Ile Ser Ile Ile Val Ala Ala Leu Gly Val Leu
85 90 95
Leu Ser Val Val Gly Gly Lys Cys Thr Asn Cys Leu Glu Asp Glu Ser
100 105 110
Ala Lys Ala Lys Thr Met Ile Val Ala Gly Val Val Phe Leu Leu Ala
115 120 125
Gly Leu Met Val Ile Val Pro Val Ser Trp Thr Ala His Asn Ile Ile
130 135 140
Gln Asp Phe Tyr Asn Pro Leu Val Ala Ser Gly Gln Lys Arg Glu Met
145 150 155 160
Gly Ala Ser Leu Tyr Val Gly Trp Ala Ala Ser Gly Leu Leu Leu Leu
165 170 175
Gly Gly Gly Leu Leu Cys Cys Asn Cys Pro Pro Arg Thr Asp Lys Pro
180 185 190
Tyr Ser Ala Lys Tyr Ser Ala Ala Arg Ser Ala Ala Ala Ser Asn Tyr
195 200 205
Val

<210> 46
<211> 1009
<212> DNA
<213> Homo sapiens

<400> 46
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gtaactgatg gacagccgag gcagcccctt aggcggctta ggcctcccct gtggagcatc 180
cctgaggcgg actccggcca gcccgagtga tgcgatccaa agagcactcc cgggtaggaa 240
attgccccgg tggaatgcct caccagagca gcgtgtagca gttccctgtg gaggattaac 300
acagtggctg aacaccggga aggaactggc acttggagtc cggacatctg aaacttggta 360

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atgtgtgtgg tgtgggtgtg gtgttttgtc tcgaagaagc atgggtcagg tacaaataag   660
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aggtaacacc aattctaagt taatttgaag tttgcttaaa gttaacagtg taacatgtat   900
tatggtaact tctaatcttg tggccttaga cagtctagtc caaaggcata aagaaagttt   960
gctttaaaaa aaaaaaaaag gaatggttat cttcaaaaaa aaaaaaaaa              1009
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<210> 47
<211> 1250
<212> DNA
<213> Homo sapiens

<400> 47

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cgccaggccc agcggccccg gcccctcgtc tccccgcacc cggagccacc cggtggagcg    180
ggccttgccg cggcagccat gtccatgggc ctggagatca cgggcaccgc gctggccgtg    240
ctgggctggc tgggcaccat cgtgtgctgc gcgttgccca tgtggcgcgt gtcggccttc    300
atcggcagca acatcatcac gtcgcagaac atctgggagg gcctgtggat gaactgcgtg    360
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<210> 48
<211> 220
<212> PRT
<213> Homo sapiens

<400> 48

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Ala Phe Ile Gly Ser Asn Ile Ile Thr Ser Gln Asn Ile Trp Glu Gly
        35                  40                  45
Leu Trp Met Asn Cys Val Val Gln Ser Thr Gly Gln Met Gln Cys Lys
    50                  55                  60
Val Tyr Asp Ser Leu Leu Ala Leu Pro Gln Asp Leu Gln Ala Ala Arg
65                  70                  75                  80
Ala Leu Ile Val Val Ala Ile Leu Leu Ala Ala Phe Gly Leu Leu Val
                85                  90                  95
Ala Leu Val Gly Ala Gln Cys Thr Asn Cys Val Gln Asp Asp Thr Ala
            100                 105                 110
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Lys Ala Lys Ile Thr Ile Val Ala Gly Val Leu Phe Leu Leu Ala Ala
115 120 125
Leu Leu Thr Leu Val Pro Val Ser Trp Ser Ala Asn Thr Ile Ile Arg
130 135 140
Asp Phe Tyr Asn Pro Val Val Pro Glu Ala Gln Lys Arg Glu Met Gly
145 150 155 160
Ala Gly Leu Tyr Val Gly Trp Ala Ala Ala Ala Leu Gln Leu Leu Gly
165 170 175
Gly Ala Leu Leu Cys Cys Ser Cys Pro Pro Arg Glu Lys Lys Tyr Thr
180 185 190
Ala Thr Lys Val Val Tyr Ser Ala Pro Arg Ser Thr Gly Pro Gly Ala
195 200 205
Ser Leu Gly Thr Gly Tyr Asp Arg Lys Asp Tyr Val
210 215 220

<210> 49
<211> 3321
<212> DNA
<213> Homo sapiens

<400> 49
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gaaaagaaac ttatttctgt tgacacggaa cattccaata tctatcttca aaatggccca 180
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tcacatggaa taacttacta taaggaacat gagggggcca tctaccctga taacaccaca 420
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gccactgaag aacaaagtcc tggggaagga gatggcaatt gtgtgactag gatttaccat 540
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cattaaaaga gactggagca t 3321

<210> 50
<211> 1065
<212> PRT
<213> Homo sapiens

<400> 50
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Trp Asp Tyr Ala Ser Asp His Gly Glu Lys Lys Leu Ile Ser Val Asp
35 40 45
Thr Glu His Ser Asn Ile Tyr Leu Gln Asn Gly Pro Asp Arg Ile Gly
50 55 60
Arg Leu Tyr Lys Lys Ala Leu Tyr Leu Gln Tyr Thr Asp Glu Thr Phe
65 70 75 80
Arg Thr Thr Ile Glu Lys Pro Val Trp Leu Gly Phe Leu Gly Pro Ile
85 90 95
Ile Lys Ala Glu Thr Gly Asp Lys Val Tyr Val His Leu Lys Asn Leu
100 105 110
Ala Ser Arg Pro Tyr Thr Phe His Ser His Gly Ile Thr Tyr Tyr Lys
115 120 125
Glu His Glu Gly Ala Ile Tyr Pro Asp Asn Thr Thr Asp Phe Gln Arg
130 135 140
Ala Asp Asp Lys Val Tyr Pro Gly Glu Gln Tyr Thr Tyr Met Leu Leu
145 150 155 160
Ala Thr Glu Glu Gln Ser Pro Gly Glu Gly Asp Gly Asn Cys Val Thr
165 170 175
Arg Ile Tyr His Ser His Ile Asp Ala Pro Lys Asp Ile Ala Ser Gly
180 185 190
Leu Ile Gly Pro Leu Ile Ile Cys Lys Lys Asp Ser Leu Asp Lys Glu
195 200 205
Lys Glu Lys His Ile Asp Arg Glu Phe Val Val Met Phe Ser Val Val
210 215 220
Asp Glu Asn Phe Ser Trp Tyr Leu Glu Asp Asn Ile Lys Thr Tyr Cys
225 230 235 240
Ser Glu Pro Glu Lys Val Asp Lys Asp Asn Glu Asp Phe Gln Glu Ser
245 250 255
Asn Arg Met Tyr Ser Val Asn Gly Tyr Thr Phe Gly Ser Leu Pro Gly
260 265 270
Leu Ser Met Cys Ala Glu Asp Arg Val Lys Trp Tyr Leu Phe Gly Met
275 280 285

Gly Asn Glu Val Asp Val His Ala Ala Phe Phe His Gly Gln Ala Leu
290 295 300
Thr Asn Lys Asn Tyr Arg Ile Asp Thr Ile Asn Leu Phe Pro Ala Thr
305 310 315 320
Leu Phe Asp Ala Tyr Met Val Ala Gln Asn Pro Gly Glu Trp Met Leu
325 330 335
Ser Cys Gln Asn Leu Asn His Leu Lys Ala Gly Leu Gln Ala Phe Phe
340 345 350
Gln Val Gln Glu Cys Asn Lys Ser Ser Ser Lys Asp Asn Ile Arg Gly
355 360 365
Lys His Val Arg His Tyr Tyr Ile Ala Ala Glu Glu Ile Ile Trp Asn
370 375 380
Tyr Ala Pro Ser Gly Ile Asp Ile Phe Thr Lys Glu Asn Leu Thr Ala
385 390 395 400
Pro Gly Ser Asp Ser Ala Val Phe Phe Glu Gln Gly Thr Thr Arg Ile
405 410 415
Gly Gly Ser Tyr Lys Lys Leu Val Tyr Arg Glu Tyr Thr Asp Ala Ser
420 425 430
Phe Thr Asn Arg Lys Glu Arg Gly Pro Glu Glu Glu His Leu Gly Ile
435 440 445
Leu Gly Pro Val Ile Trp Ala Glu Val Gly Asp Thr Ile Arg Val Thr
450 455 460
Phe His Asn Lys Gly Ala Tyr Pro Leu Ser Ile Glu Pro Ile Gly Val
465 470 475 480
Arg Phe Asn Lys Asn Asn Glu Gly Thr Tyr Tyr Ser Pro Asn Tyr Asn
485 490 495
Pro Gln Ser Arg Ser Val Pro Pro Ser Ala Ser His Val Ala Pro Thr
500 505 510
Glu Thr Phe Thr Tyr Glu Trp Thr Val Pro Lys Glu Val Gly Pro Thr
515 520 525
Asn Ala Asp Pro Val Cys Leu Ala Lys Met Tyr Tyr Ser Ala Val Asp
530 535 540
Pro Thr Lys Asp Ile Phe Thr Gly Leu Ile Gly Pro Met Lys Ile Cys
545 550 555 560
Lys Lys Gly Ser Leu His Ala Asn Gly Arg Gln Lys Asp Val Asp Lys
565 570 575
Glu Phe Tyr Leu Phe Pro Thr Val Phe Asp Glu Asn Glu Ser Leu Leu
580 585 590
Leu Glu Asp Asn Ile Arg Met Phe Thr Thr Ala Pro Asp Gln Val Asp
595 600 605
Lys Glu Asp Glu Asp Phe Gln Glu Ser Asn Lys Met His Ser Met Asn
610 615 620
Gly Phe Met Tyr Gly Asn Gln Pro Gly Leu Thr Met Cys Lys Gly Asp
625 630 635 640
Ser Val Val Trp Tyr Leu Phe Ser Ala Gly Asn Glu Ala Asp Val His
645 650 655
Gly Ile Tyr Phe Ser Gly Asn Thr Tyr Leu Trp Arg Gly Glu Arg Arg
660 665 670
Asp Thr Ala Asn Leu Phe Pro Gln Thr Ser Leu Thr Leu His Met Trp
675 680 685
Pro Asp Thr Glu Gly Thr Phe Asn Val Glu Cys Leu Thr Thr Asp His
690 695 700
Tyr Thr Gly Gly Met Lys Gln Lys Tyr Thr Val Asn Gln Cys Arg Arg
705 710 715 720
Gln Ser Glu Asp Ser Thr Phe Tyr Leu Gly Glu Arg Thr Tyr Tyr Ile
725 730 735
Ala Ala Val Glu Val Glu Trp Asp Tyr Ser Pro Gln Arg Glu Trp Glu
740 745 750
Lys Glu Leu His His Leu Gln Glu Gln Asn Val Ser Asn Ala Phe Leu
755 760 765

Asp Lys Gly Glu Phe Tyr Ile Gly Ser Lys Tyr Lys Lys Val Val Tyr
770 775 780
Arg Gln Tyr Thr Asp Ser Thr Phe Arg Val Pro Val Glu Arg Lys Ala
785 790 795 800
Glu Glu Glu His Leu Gly Ile Leu Gly Pro Gln Leu His Ala Asp Val
805 810 815
Gly Asp Lys Val Lys Ile Ile Phe Lys Asn Met Ala Thr Arg Pro Tyr
820 825 830
Ser Ile His Ala His Gly Val Gln Thr Glu Ser Ser Thr Val Thr Pro
835 840 845
Thr Leu Pro Gly Glu Thr Leu Thr Tyr Val Trp Lys Ile Pro Glu Arg
850 855 860
Ser Gly Ala Gly Thr Glu Asp Ser Ala Cys Ile Pro Trp Ala Tyr Tyr
865 870 875 880
Ser Thr Val Asp Gln Val Lys Asp Leu Tyr Ser Gly Leu Ile Gly Pro
885 890 895
Leu Ile Val Cys Arg Arg Pro Tyr Leu Lys Val Phe Asn Pro Arg Arg
900 905 910
Lys Leu Glu Phe Ala Leu Leu Phe Leu Val Phe Asp Glu Asn Glu Ser
915 920 925
Trp Tyr Leu Asp Asp Asn Ile Lys Thr Tyr Ser Asp His Pro Glu Lys
930 935 940
Val Asn Lys Asp Asp Glu Glu Phe Ile Glu Ser Asn Lys Met His Ala
945 950 955 960
Ile Asn Gly Arg Met Phe Gly Asn Leu Gln Gly Leu Thr Met His Val
965 970 975
Gly Asp Glu Val Asn Trp Tyr Leu Met Gly Met Gly Asn Glu Ile Asp
980 985 990
Leu His Thr Val His Phe His Gly His Ser Phe Gln Tyr Lys His Arg
995 1000 1005
Gly Val Tyr Ser Ser Asp Val Phe Asp Ile Phe Pro Gly Thr Tyr Gln
1010 1015 1020
Thr Leu Glu Met Phe Pro Arg Thr Pro Gly Ile Trp Leu Leu His Cys
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1045 1050 1055
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1060 1065

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<211> 1603
<212> DNA
<213> Homo sapiens

<400> 51
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gaccaggtgg aggctttgtc cctaatttcc agctctttga gaaaggggat gtcaatggag 480
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ctgtgtgcct gcagctgtgt agtgctggac agtgacaacc ctttctctcc agttctccac    1080
tccaatgata atagttcact tacacctaaa cccaaaggaa aaaccagctc taggtccaat    1140
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caccctgctc cttcggagga cgtgccctca cccctcactg gtccactggc ttgagactca    1560
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<210> 52
<211> 226
<212> PRT
<213> Homo sapiens

<220>
<221> VARIANT
<222> 0-00
<223> Xaa = any amino acid

<400> 52

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Met Ala Arg Leu Leu Gln Ala Ser Cys Leu Leu Ser Leu Leu Leu Ala
 1               5                  10                  15
Gly Phe Val Ser Gln Ser Arg Gly Gln Glu Lys Ser Lys Met Asp Cys
            20                  25                  30
His Gly Gly Ile Ser Gly Thr Ile Tyr Glu Tyr Gly Ala Leu Thr Ile
        35                  40                  45
Asp Gly Glu Glu Tyr Ile Pro Phe Lys Gln Tyr Ala Gly Lys Tyr Val
    50                  55                  60
Leu Phe Val Asn Val Ala Ser Tyr Xaa Gly Leu Thr Gly Gln Tyr Ile
65                  70                  75                  80
Glu Leu Asn Ala Leu Gln Glu Glu Leu Ala Pro Phe Gly Leu Val Ile
                85                  90                  95
Leu Gly Phe Pro Cys Asn Gln Phe Gly Lys Gln Glu Pro Gly Glu Asn
            100                 105                 110
Ser Glu Ile Leu Pro Thr Leu Lys Tyr Val Arg Pro Gly Gly Gly Phe
        115                 120                 125
Val Pro Asn Phe Gln Leu Phe Glu Lys Gly Asp Val Asn Gly Glu Lys
    130                 135                 140
Glu Gln Lys Phe Tyr Thr Phe Leu Lys Asn Ser Cys Pro Pro Thr Ser
145                 150                 155                 160
Glu Leu Leu Gly Thr Ser Asp Arg Leu Phe Trp Glu Pro Met Lys Val
                165                 170                 175
His Asp Ile Arg Trp Asn Phe Glu Lys Phe Leu Val Gly Pro Asp Gly
            180                 185                 190
Ile Pro Ile Met Arg Trp His His Arg Thr Thr Val Ser Asn Val Lys
        195                 200                 205
Met Asp Ile Leu Ser Tyr Met Arg Arg Gln Ala Ala Leu Gly Val Lys
    210                 215                 220
Arg Lys
225
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<210> 53
<211> 399
<212> DNA
<213> Homo sapiens

<400> 53
atgaagtcca gcggcctctt ccccttcctg gtgctgcttg ccctgggaac tctggcacct 60
tgggctgtgg aaggctctgg aaagtccttc aaagctggag tctgtcctcc taagaaatct 120
gcccagtgcc ttagatacaa gaaacctgag tgccagagtg actggcagtg tccagggaag 180
aagagatgtt gtcctgacac ttgtggcatc aaatgcctgg atcctgttga caccccaaac 240
ccaacaagga ggaagcctgg gaagtgccca gtgacttatg gccaatgttt gatgcttaac 300
ccccccaatt tctgtgagat ggatggccag tgcaagcgtg acttgaagtg ttgcatgggc 360
atgtgtggga aatcctgcgt ttcccctgtg aaagcttga 399

<210> 54
<211> 132
<212> PRT
<213> Homo sapiens

<400> 54
Met Lys Ser Ser Gly Leu Phe Pro Phe Leu Val Leu Leu Ala Leu Gly
1 5 10 15
Thr Leu Ala Pro Trp Ala Val Glu Gly Ser Gly Lys Ser Phe Lys Ala
20 25 30
Gly Val Cys Pro Pro Lys Lys Ser Ala Gln Cys Leu Arg Tyr Lys Lys
35 40 45
Pro Glu Cys Gln Ser Asp Trp Gln Cys Pro Gly Lys Lys Arg Cys Cys
50 55 60
Pro Asp Thr Cys Gly Ile Lys Cys Leu Asp Pro Val Asp Thr Pro Asn
65 70 75 80
Pro Thr Arg Arg Lys Pro Gly Lys Cys Pro Val Thr Tyr Gly Gln Cys
85 90 95
Leu Met Leu Asn Pro Pro Asn Phe Cys Glu Met Asp Gly Gln Cys Lys
100 105 110
Arg Asp Leu Lys Cys Cys Met Gly Met Cys Gly Lys Ser Cys Val Ser
115 120 125
Pro Val Lys Ala
130

<210> 55
<211> 3557
<212> DNA
<213> Homo sapiens

<400> 55
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tactctggtt gcagactgac cttgctcagg cctgagaagg atggggcagc caccagagtg 120
gatgctgtct gcacccatcg tcctgacccc aaaagccctg gactggacag agagcggctg 180
tactggaagc tgagccagct gacccacggc atcactgagc tgggccccta caccctggac 240
aggcacagtc tctatgtcaa tggtttcacc catcagagct ctatgacgac caccagaact 300
cctgatacct ccacaatgca cctggcaacc tcgagaactc cagcctccct gtctggacct 360
acgaccgcca gccctctcct ggtgctattc acaattaact tcaccatcac taacctgcgg 420
tatgaggaga acatgcatca ccctggctct agaaagttta acaccacgga gagagtcctt 480
cagggtctgc tcaggcctgt gttcaagaac accagtgttg gccctctgta ctctggctgc 540
agactgacct tgctcaggcc caagaaggat ggggcagcca ccaaagtgga tgccatctgc 600
acctaccgcc ctgatcccaa aagccctgga ctggacagag agcagctata ctgggagctg 660
agccagctaa cccacagcat cactgagctg ggcccctaca ccctggacag ggacagtctc 720
tatgtcaatg gtttcacaca gcggagctct gtgcccacca ctagcattcc tgggaccccc 780
acagtggacc tgggaacatc tgggactcca gtttctaaac ctggtccctc ggctgccagc 840
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aggtccctgt tcaagagcac cagtgttggc cctctgtact ctggctgcag actgactttg 1020
ctcaggcctg aaaaggatgg gacagccact ggagtggatg ccatctgcac ccaccaccct 1080
gaccccaaaa gccctaggct ggacagagag cagctgtatt gggagctgag ccagctgacc 1140
cacaatatca ctgagctggg ccactatgcc ctggacaacg acagcctctt tgtcaatggt 1200

ttcactcatc ggagctctgt gtccaccacc agcactcctg ggacccccac agtgtatctg 1260
ggagcatcta agactccagc ctcgatattt ggcccttcag ctgccagcca tctcctgata 1320
ctattcaccc tcaacttcac catcactaac ctgcggtatg aggagaacat gtggcctggc 1380
tccaggaagt tcaacactac agagagggtc cttcagggcc tgctaaggcc cttgttcaag 1440
aacaccagtg ttggccctct gtactctggc tccaggctga ccttgctcag gccagagaaa 1500
gatggggaag ccaccggagt ggatgccatc tgcacccacc gccctgaccc cacaggccct 1560
gggctggaca gagagcagct gtatttggag ctgagccagc tgacccacag catcactgag 1620
ctgggcccct acacactgga cagggacagt ctctatgtca atggtttcac ccatcggagc 1680
tctgtaccca ccaccagcac cggggtggtc agcgaggagc cattcacact gaacttcacc 1740
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acagacaacg tcatgaagca cctgctcagt cctttgttcc agaggagcag cctgggtgca 1860
cggtacacag gctgcagggt catcgcacta aggtctgtga agaacggtgc tgagacacgg 1920
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gtgttccatg agctgagcca gcagacccat ggcatcaccc ggctgggccc ctactctctg 2040
gacaaagaca gcctctacct taacggttac aatgaacctg gtctagatga gcctcctaca 2100
actcccaagc cagccaccac attcctgcct cctctgtcag aagccacaac agccatgggg 2160
taccacctga agaccctcac actcaacttc accatctcca atctccagta ttcaccagat 2220
atgggcaagg gctcagctac attcaactcc accgaggggg tccttcagca cctgctcaga 2280
cccttgttcc agaagagcag catgggcccc ttctacttgg gttgccaact gatctccctc 2340
aggcctgaga aggatggggc agccactggt gtggacacca cctgcaccta ccaccctgac 2400
cctgtgggcc ccgggctgga catacagcag ctttactggg agctgagtca gctgacccat 2460
ggtgtcaccc aactgggctt ctatgtcctg gacagggata gcctcttcat caatggctat 2520
gcaccccaga atttatcaat ccggggcgag taccagataa atttccacat tgtcaactgg 2580
aacctcagta atccagaccc cacatcctca gagtacatca ccctgctgag ggacatccag 2640
gacaaggtca ccacactcta caaaggcagt caactacatg acacattccg cttctgcctg 2700
gtcaccaact tgacgatgga ctccgtgttg gtcactgtca aggcattgtt ctcctccaat 2760
ttggacccca gcctggtgga gcaagtcttt ctagataaga ccctgaatgc ctcattccat 2820
tggctgggct ccacctacca gttggtggac atccatgtga cagaaatgga gtcatcagtt 2880
tatcaaccaa caagcagctc cagcacccag cacttctacc cgaatttcac catcaccaac 2940
ctaccatatt cccaggacaa agcccagcca ggcaccacca attaccagag gaacaaaagg 3000
aatattgagg atgcgctcaa ccaactcttc cgaaacagca gcatcaagag ttatttttct 3060
gactgtcaag tttcaacatt caggtctgtc cccaacaggc accacaccgg ggtggactcc 3120
ctgtgtaact tctcgccact ggctcggaga gtagacagag ttgccatcta tgaggaattt 3180
ctgcggatga cccggaatgg tacccagctg cagaacttca ccctggacag gagcagtgtc 3240
cttgtggatg ggtattctcc caacagaaat gagcccttaa ctgggaattc tgaccttccc 3300
ttctgggctg tcatcttcat cggcttggca ggactcctgg gactcatcac atgcctgatc 3360
tgcggtgtcc tggtgaccac ccgccggcgg aagaaggaag gagaatacaa cgtccagcaa 3420
cagtgcccag gctactacca gtcacaccta gacctggagg atctgcaatg actggaactt 3480
gccggtgcct ggggtgcctt tcccccagcc agggtccaaa gaagcttggc tggggcagaa 3540
ataaaccata ttggtcg 3557

<210> 56
<211> 1148
<212> PRT
<213> Homo sapiens

<400> 56
Met Pro Leu Phe Lys Asn Thr Ser Val Ser Ser Leu Tyr Ser Gly Cys
1 5 10 15
Arg Leu Thr Leu Leu Arg Pro Glu Lys Asp Gly Ala Ala Thr Arg Val
20 25 30
Asp Ala Val Cys Thr His Arg Pro Asp Pro Lys Ser Pro Gly Leu Asp
35 40 45
Arg Glu Arg Leu Tyr Trp Lys Leu Ser Gln Leu Thr His Gly Ile Thr
50 55 60
Glu Leu Gly Pro Tyr Thr Leu Asp Arg His Ser Leu Tyr Val Asn Gly
65 70 75 80
Phe Thr His Gln Ser Ser Met Thr Thr Thr Arg Thr Pro Asp Thr Ser
85 90 95

Thr Met His Leu Ala Thr Ser Arg Thr Pro Ala Ser Leu Ser Gly Pro
100 105 110
Thr Thr Ala Ser Pro Leu Leu Val Leu Phe Thr Ile Asn Phe Thr Ile
115 120 125
Thr Asn Leu Arg Tyr Glu Glu Asn Met His His Pro Gly Ser Arg Lys
130 135 140
Phe Asn Thr Thr Glu Arg Val Leu Gln Gly Leu Leu Arg Pro Val Phe
145 150 155 160
Lys Asn Thr Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg Leu Thr Leu
165 170 175
Leu Arg Pro Lys Lys Asp Gly Ala Ala Thr Lys Val Asp Ala Ile Cys
180 185 190
Thr Tyr Arg Pro Asp Pro Lys Ser Pro Gly Leu Asp Arg Glu Gln Leu
195 200 205
Tyr Trp Glu Leu Ser Gln Leu Thr His Ser Ile Thr Glu Leu Gly Pro
210 215 220
Tyr Thr Leu Asp Arg Asp Ser Leu Tyr Val Asn Gly Phe Thr Gln Arg
225 230 235 240
Ser Ser Val Pro Thr Thr Ser Ile Pro Gly Thr Pro Thr Val Asp Leu
245 250 255
Gly Thr Ser Gly Thr Pro Val Ser Lys Pro Gly Pro Ser Ala Ala Ser
260 265 270
Pro Leu Leu Val Leu Phe Thr Leu Asn Phe Thr Ile Thr Asn Leu Arg
275 280 285
Tyr Glu Glu Asn Met Gln His Pro Gly Ser Arg Lys Phe Asn Thr Thr
290 295 300
Glu Arg Val Leu Gln Gly Leu Leu Arg Ser Leu Phe Lys Ser Thr Ser
305 310 315 320
Val Gly Pro Leu Tyr Ser Gly Cys Arg Leu Thr Leu Leu Arg Pro Glu
325 330 335
Lys Asp Gly Thr Ala Thr Gly Val Asp Ala Ile Cys Thr His His Pro
340 345 350
Asp Pro Lys Ser Pro Arg Leu Asp Arg Glu Gln Leu Tyr Trp Glu Leu
355 360 365
Ser Gln Leu Thr His Asn Ile Thr Glu Leu Gly His Tyr Ala Leu Asp
370 375 380
Asn Asp Ser Leu Phe Val Asn Gly Phe Thr His Arg Ser Ser Val Ser
385 390 395 400
Thr Thr Ser Thr Pro Gly Thr Pro Thr Val Tyr Leu Gly Ala Ser Lys
405 410 415
Thr Pro Ala Ser Ile Phe Gly Pro Ser Ala Ala Ser His Leu Leu Ile
420 425 430
Leu Phe Thr Leu Asn Phe Thr Ile Thr Asn Leu Arg Tyr Glu Glu Asn
435 440 445
Met Trp Pro Gly Ser Arg Lys Phe Asn Thr Thr Glu Arg Val Leu Gln
450 455 460
Gly Leu Leu Arg Pro Leu Phe Lys Asn Thr Ser Val Gly Pro Leu Tyr
465 470 475 480
Ser Gly Ser Arg Leu Thr Leu Leu Arg Pro Glu Lys Asp Gly Glu Ala
485 490 495
Thr Gly Val Asp Ala Ile Cys Thr His Arg Pro Asp Pro Thr Gly Pro
500 505 510
Gly Leu Asp Arg Glu Gln Leu Tyr Leu Glu Leu Ser Gln Leu Thr His
515 520 525
Ser Ile Thr Glu Leu Gly Pro Tyr Thr Leu Asp Arg Asp Ser Leu Tyr
530 535 540
Val Asn Gly Phe Thr His Arg Ser Ser Val Pro Thr Thr Ser Thr Gly
545 550 555 560
Val Val Ser Glu Glu Pro Phe Thr Leu Asn Phe Thr Ile Asn Asn Leu
565 570 575

```
Arg Tyr Met Ala Asp Met Gly Gln Pro Gly Ser Leu Lys Phe Asn Ile
            580                 585                 590
Thr Asp Asn Val Met Lys His Leu Leu Ser Pro Leu Phe Gln Arg Ser
        595                 600                 605
Ser Leu Gly Ala Arg Tyr Thr Gly Cys Arg Val Ile Ala Leu Arg Ser
    610                 615                 620
Val Lys Asn Gly Ala Glu Thr Arg Val Asp Leu Leu Cys Thr Tyr Leu
625                 630                 635                 640
Gln Pro Leu Ser Gly Pro Gly Leu Pro Ile Lys Gln Val Phe His Glu
                645                 650                 655
Leu Ser Gln Gln Thr His Gly Ile Thr Arg Leu Gly Pro Tyr Ser Leu
            660                 665                 670
Asp Lys Asp Ser Leu Tyr Leu Asn Gly Tyr Asn Glu Pro Gly Leu Asp
        675                 680                 685
Glu Pro Pro Thr Thr Pro Lys Pro Ala Thr Thr Phe Leu Pro Pro Leu
    690                 695                 700
Ser Glu Ala Thr Thr Ala Met Gly Tyr His Leu Lys Thr Leu Thr Leu
705                 710                 715                 720
Asn Phe Thr Ile Ser Asn Leu Gln Tyr Ser Pro Asp Met Gly Lys Gly
                725                 730                 735
Ser Ala Thr Phe Asn Ser Thr Glu Gly Val Leu Gln His Leu Leu Arg
            740                 745                 750
Pro Leu Phe Gln Lys Ser Ser Met Gly Pro Phe Tyr Leu Gly Cys Gln
        755                 760                 765
Leu Ile Ser Leu Arg Pro Glu Lys Asp Gly Ala Ala Thr Gly Val Asp
    770                 775                 780
Thr Thr Cys Thr Tyr His Pro Asp Pro Val Gly Pro Gly Leu Asp Ile
785                 790                 795                 800
Gln Gln Leu Tyr Trp Glu Leu Ser Gln Leu Thr His Gly Val Thr Gln
                805                 810                 815
Leu Gly Phe Tyr Val Leu Asp Arg Asp Ser Leu Phe Ile Asn Gly Tyr
            820                 825                 830
Ala Pro Gln Asn Leu Ser Ile Arg Gly Glu Tyr Gln Ile Asn Phe His
        835                 840                 845
Ile Val Asn Trp Asn Leu Ser Asn Pro Asp Pro Thr Ser Ser Glu Tyr
    850                 855                 860
Ile Thr Leu Leu Arg Asp Ile Gln Asp Lys Val Thr Thr Leu Tyr Lys
865                 870                 875                 880
Gly Ser Gln Leu His Asp Thr Phe Arg Phe Cys Leu Val Thr Asn Leu
                885                 890                 895
Thr Met Asp Ser Val Leu Val Thr Val Lys Ala Leu Phe Ser Ser Asn
            900                 905                 910
Leu Asp Pro Ser Leu Val Glu Gln Val Phe Leu Asp Lys Thr Leu Asn
        915                 920                 925
Ala Ser Phe His Trp Leu Gly Ser Thr Tyr Gln Leu Val Asp Ile His
    930                 935                 940
Val Thr Glu Met Glu Ser Ser Val Tyr Gln Pro Thr Ser Ser Ser Ser
945                 950                 955                 960
Thr Gln His Phe Tyr Pro Asn Phe Thr Ile Thr Asn Leu Pro Tyr Ser
                965                 970                 975
Gln Asp Lys Ala Gln Pro Gly Thr Thr Asn Tyr Gln Arg Asn Lys Arg
            980                 985                 990
Asn Ile Glu Asp Ala Leu Asn Gln Leu Phe Arg Asn Ser Ser Ile Lys
        995                 1000                1005
Ser Tyr Phe Ser Asp Cys Gln Val Ser Thr Phe Arg Ser Val Pro Asn
    1010                1015                1020
Arg His His Thr Gly Val Asp Ser Leu Cys Asn Phe Ser Pro Leu Ala
1025                1030                1035                1040
Arg Arg Val Asp Arg Val Ala Ile Tyr Glu Glu Phe Leu Arg Met Thr
                1045                1050                1055
```

```
Arg Asn Gly Thr Gln Leu Gln Asn Phe Thr Leu Asp Arg Ser Ser Val
            1060                1065                1070
Leu Val Asp Gly Tyr Ser Pro Asn Arg Asn Glu Pro Leu Thr Gly Asn
        1075                1080                1085
Ser Asp Leu Pro Phe Trp Ala Val Ile Phe Ile Gly Leu Ala Gly Leu
    1090                1095                1100
Leu Gly Leu Ile Thr Cys Leu Ile Cys Gly Val Leu Val Thr Thr Arg
1105                1110                1115                1120
Arg Arg Lys Lys Glu Gly Glu Tyr Asn Val Gln Gln Gln Cys Pro Gly
                1125                1130                1135
Tyr Tyr Gln Ser His Leu Asp Leu Glu Asp Leu Gln
            1140                1145
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<210> 57
<211> 853
<212> DNA
<213> Homo sapiens

<400> 57

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ctagtcctga cttcacttct gatgaggaag cctctctcct tagccttcag cctttcctcc      60
caccctgcca taagtaattt gatcctcaag aagttaaacc acacctcatt ggtccctggc     120
taattcacca atttacaaac agcaggaaat agaaacttaa gagaaataca cacttctgag     180
aaactgaaac gacaggggaa aggaggtctc actgagcacc gtcccagcat ccggacacca     240
cagcggccct tcgctccacg cagaaaacca cacttctcaa accttcactc aacacttcct     300
tccccaaagc cagaagatgc acaaggagga acatgaggtg gctgtgctgg gggcaccccc     360
cagcaccatc cttccaaggt ccaccgtgat caacatccac agcgagacct ccgtgcccga     420
ccatgtcgtc tggtccctgt tcaacaccct cttcttgaac tggtgctgtc tgggcttcat     480
agcattcgcc tactccgtga agtctaggga caggaagatg gttggcgacg tgaccggggc     540
ccaggcctat gcctccaccg ccaagtgcct gaacatctgg gccctgattc tgggcatcct     600
catgaccatt ggattcatcc tgtcactggt attcggctct gtgacagtct accatattat     660
gttacagata atacaggaaa aacggggtta ctagtagccg cccatagcct gcaacctttg     720
cactccactg tgcaatgctg gccctgcacg ctggggctgt tgcccctgcc cccttggtcc     780
tgcccctaga tacagcagtt tatacccaca cacctgtcta cagtgtcatt caataaagtg     840
cacgtgcttg tga                                                        853
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<210> 58
<211> 125
<212> PRT
<213> Homo sapiens

<400> 58

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Met His Lys Glu Glu His Glu Val Ala Val Leu Gly Ala Pro Pro Ser
 1               5                  10                  15
Thr Ile Leu Pro Arg Ser Thr Val Ile Asn Ile His Ser Glu Thr Ser
            20                  25                  30
Val Pro Asp His Val Val Trp Ser Leu Phe Asn Thr Leu Phe Leu Asn
        35                  40                  45
Trp Cys Cys Leu Gly Phe Ile Ala Phe Ala Tyr Ser Val Lys Ser Arg
    50                  55                  60
Asp Arg Lys Met Val Gly Asp Val Thr Gly Ala Gln Ala Tyr Ala Ser
65                  70                  75                  80
Thr Ala Lys Cys Leu Asn Ile Trp Ala Leu Ile Leu Gly Ile Leu Met
                85                  90                  95
Thr Ile Gly Phe Ile Leu Ser Leu Val Phe Gly Ser Val Thr Val Tyr
            100                 105                 110
His Ile Met Leu Gln Ile Ile Gln Glu Lys Arg Gly Tyr
        115                 120                 125
```

<210> 59
<211> 1512

<212> DNA
<213> Homo sapiens

<400> 59
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ttccggtccc ccaggacatg tccaatcagg gaagtaagta cgtcaataag gaaattcaaa      60
atgctgtcaa cggggtgaaa cagataaaga ctctcataga aaaaacaaac gaagagcgca     120
agacactgct cagcaaccta gaagaagcca agaagaagaa agaggatgcc ctaaatgaga     180
ccagggaatc agagacaaag ctgaaggagc tcccaggagt gtgcaatgag accatgatgg     240
ccctctggga agagtgtaag ccctgcctga aacagacctg catgaagttc tacgcacgcg     300
tctgcagaag tggctcaggc ctggttggcc gccagcttga ggagttcctg aaccagagct     360
cgcccttcta cttctggatg aatggtgacc gcatcgactc cctgctggag aacgaccggc     420
agcagacgca catgctggat gtcatgcagg accacttcag ccgcgcgtcc agcatcatag     480
acgagctctt ccaggacagg ttcttcaccc gggagcccca ggatacctac cactacctgc     540
ccttcagcct gccccaccgg aggcctcact tcttctttcc caagtcccgc atcgtccgca     600
gcttgatgcc cttctctccg tacgagcccc tgaacttcca cgccatgttc cagcccttcc     660
ttgagatgat acacgaggct cagcaggcca tggacatcca cttccacagc ccggccttcc     720
agcacccgcc aacagaattc atacgagaag gcgacgatga ccggactgtg tgccgggaga     780
tccgccacaa ctccacgggc tgcctgcgga tgaaggacca gtgtgacaag tgccgggaga     840
tcttgtctgt ggactgttcc accaacaacc cctcccaggc taagctgcgg cgggagctcg     900
acgaatccct ccaggtcgct gagaggttga ccaggaaata caacgagctg ctaaagtcct     960
accagtggaa gatgctcaac acctcctcct tgctggagca gctgaacgag cagtttaact    1020
gggtgtcccg gctggcaaac ctcacgcaag gcgaagacca gtactatctg cgggtcacca    1080
cggtggcttc ccacacttct gactcggacg ttccttccgg tgtcactgag gtggtcgtga    1140
agctctttga ctctgatccc atcactgtga cggtccctgt agaagtctcc aggaagaacc    1200
ctaaatttat ggagaccgtg gcggagaaag cgctgcagga ataccgcaaa aagcaccggg    1260
aggagtgaga tgtggatgtt gcttttgcac ctacgggggc atctgagtcc agctcccccc    1320
aagatgagct gcagcccccc agagagagct ctgcacgtca ccaagtaacc aggccccagc    1380
ctccaggccc ccaactccgc ccagcctctc cccgctctgg atcctgcact ctaacactcg    1440
actctgctgc tcatgggaag aacagaattg ctcctgcatg caactaattc aataaaactg    1500
tcttgtgagc tg                                                        1512
```

<210> 60
<211> 416
<212> PRT
<213> Homo sapiens

<400> 60
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Met Ser Asn Gln Gly Ser Lys Tyr Val Asn Lys Glu Ile Gln Asn Ala
1               5                   10                  15
Val Asn Gly Val Lys Gln Ile Lys Thr Leu Ile Glu Lys Thr Asn Glu
            20                  25                  30
Glu Arg Lys Thr Leu Leu Ser Asn Leu Glu Glu Ala Lys Lys Lys Lys
        35                  40                  45
Glu Asp Ala Leu Asn Glu Thr Arg Glu Ser Glu Thr Lys Leu Lys Glu
    50                  55                  60
Leu Pro Gly Val Cys Asn Glu Thr Met Met Ala Leu Trp Glu Glu Cys
65                  70                  75                  80
Lys Pro Cys Leu Lys Gln Thr Cys Met Lys Phe Tyr Ala Arg Val Cys
                85                  90                  95
Arg Ser Gly Ser Gly Leu Val Gly Arg Gln Leu Glu Glu Phe Leu Asn
            100                 105                 110
Gln Ser Ser Pro Phe Tyr Phe Trp Met Asn Gly Asp Arg Ile Asp Ser
        115                 120                 125
Leu Leu Glu Asn Asp Arg Gln Gln Thr His Met Leu Asp Val Met Gln
    130                 135                 140
Asp His Phe Ser Arg Ala Ser Ser Ile Ile Asp Glu Leu Phe Gln Asp
145                 150                 155                 160
Arg Phe Phe Thr Arg Glu Pro Gln Asp Thr Tyr His Tyr Leu Pro Phe
                165                 170                 175
```

```
Ser Leu Pro His Arg Arg Pro His Phe Phe Phe Pro Lys Ser Arg Ile
            180                 185                 190
Val Arg Ser Leu Met Pro Phe Ser Pro Tyr Glu Pro Leu Asn Phe His
        195                 200                 205
Ala Met Phe Gln Pro Phe Leu Glu Met Ile His Glu Ala Gln Gln Ala
    210                 215                 220
Met Asp Ile His Phe His Ser Pro Ala Phe Gln His Pro Pro Thr Glu
225                 230                 235                 240
Phe Ile Arg Glu Gly Asp Asp Asp Arg Thr Val Cys Arg Glu Ile Arg
                245                 250                 255
His Asn Ser Thr Gly Cys Leu Arg Met Lys Asp Gln Cys Asp Lys Cys
            260                 265                 270
Arg Glu Ile Leu Ser Val Asp Cys Ser Thr Asn Asn Pro Ser Gln Ala
        275                 280                 285
Lys Leu Arg Arg Glu Leu Asp Glu Ser Leu Gln Val Ala Glu Arg Leu
    290                 295                 300
Thr Arg Lys Tyr Asn Glu Leu Leu Lys Ser Tyr Gln Trp Lys Met Leu
305                 310                 315                 320
Asn Thr Ser Ser Leu Leu Glu Gln Leu Asn Glu Gln Phe Asn Trp Val
                325                 330                 335
Ser Arg Leu Ala Asn Leu Thr Gln Gly Glu Asp Gln Tyr Tyr Leu Arg
            340                 345                 350
Val Thr Thr Val Ala Ser His Thr Ser Asp Ser Asp Val Pro Ser Gly
        355                 360                 365
Val Thr Glu Val Val Val Lys Leu Phe Asp Ser Asp Pro Ile Thr Val
    370                 375                 380
Thr Val Pro Val Glu Val Ser Arg Lys Asn Pro Lys Phe Met Glu Thr
385                 390                 395                 400
Val Ala Glu Lys Ala Leu Gln Glu Tyr Arg Lys Lys His Arg Glu Glu
                405                 410                 415
```

<210> 61
<211> 1564
<212> DNA
<213> Homo sapiens

<400> 61

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cggacgcgtg ggcggacgcg tgggcgaggg cgcgagtgag gagcagaccc aggcatcgcg     60
cgccgagaag gccggagcgt cggcacctga acgcgaggcg ctccattgcg cgtgcgcgtt    120
gaggggcttc ccgcacctga tcgcgagacc ccaacggctg gtggcgtcgc ctgcgcgggc    180
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gaccaaggag gagtgcctca agaaatgtgc cactgtcaca gagaatgcca cgggtgacct    660
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tgaagaccac tccagcgata tgttcaacta tgaagaatac tgcaccgcca acgcagtcac    780
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taacttcatc tatggaggct gccggggcaa taagaacagc taccgctctg aggaggcctg    900
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<210> 62
<211> 252
<212> PRT
<213> Homo sapiens

<400> 62
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Leu Gly Ser Leu Leu Leu Ser Gly Val Leu Ala Ala Asp Arg Glu Arg
20 25 30
Ser Ile His Asp Phe Cys Leu Val Ser Lys Val Val Gly Arg Cys Arg
35 40 45
Ala Ser Met Pro Lys Trp Trp Tyr Asn Val Thr Asp Gly Ser Cys Gln
50 55 60
Leu Phe Val Tyr Gly Gly Cys Asp Gly Asn Ser Asn Asn Tyr Leu Thr
65 70 75 80
Lys Glu Glu Cys Leu Lys Lys Cys Ala Thr Val Thr Glu Asn Ala Thr
85 90 95
Gly Asp Leu Ala Thr Ser Arg Asn Ala Ala Asp Ser Ser Val Pro Ser
100 105 110
Ala Pro Arg Arg Gln Asp Ser Glu Asp His Ser Ser Asp Met Phe Asn
115 120 125
Tyr Glu Glu Tyr Cys Thr Ala Asn Ala Val Thr Gly Pro Cys Arg Ala
130 135 140
Ser Phe Pro Arg Trp Tyr Phe Asp Val Glu Arg Asn Ser Cys Asn Asn
145 150 155 160
Phe Ile Tyr Gly Gly Cys Arg Gly Asn Lys Asn Ser Tyr Arg Ser Glu
165 170 175
Glu Ala Cys Met Leu Arg Cys Phe Arg Gln Gln Glu Asn Pro Pro Leu
180 185 190
Pro Leu Gly Ser Lys Val Val Val Leu Ala Gly Leu Phe Val Met Val
195 200 205
Leu Ile Leu Phe Leu Gly Ala Ser Met Val Tyr Leu Ile Arg Val Ala
210 215 220
Arg Arg Asn Gln Glu Arg Ala Leu Arg Thr Val Trp Ser Ser Gly His
225 230 235 240
Asp Lys Glu Gln Leu Val Lys Asn Thr Tyr Val Leu
245 250

<210> 63
<211> 1147
<212> DNA
<213> Homo sapiens

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caggcctggg gcgagcggct gcgcgcgcgg atggaggaga tgggcagccg gacccgcgac      780
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cagcagatac gcctgcaggc cgaggccttc caggcccgcc tcaagagctg gttcgagccc      900
ctggtggaag acatgcagcg ccagtgggcc gggctggtgg agaaggtgca ggctgccgtg      960
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cgaccccacg ccaccccgtg cctcctgcct ccgcgcagcc tgcagcggga gaccctgtcc     1080
ccgccccagc cgtcctcctg gggtggaccc tagtttaata aagattcacc aagtttcacg     1140
caaaaaa                                                               1147
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<210> 64
<211> 317
<212> PRT
<213> Homo sapiens

<400> 64

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            20                  25                  30
Arg Gln Gln Thr Glu Trp Gln Ser Gly Gln Arg Trp Glu Leu Ala Leu
        35                  40                  45
Gly Arg Phe Trp Asp Tyr Leu Arg Trp Val Gln Thr Leu Ser Glu Gln
    50                  55                  60
Val Gln Glu Glu Leu Leu Ser Ser Gln Val Thr Gln Glu Leu Arg Ala
65                  70                  75                  80
Leu Met Asp Glu Thr Met Lys Glu Leu Lys Ala Tyr Lys Ser Glu Leu
                85                  90                  95
Glu Glu Gln Leu Thr Pro Val Ala Glu Glu Thr Arg Ala Arg Leu Ser
            100                 105                 110
Lys Glu Leu Gln Ala Ala Gln Ala Arg Leu Gly Ala Asp Met Glu Asp
        115                 120                 125
Val Cys Gly Arg Leu Val Gln Tyr Arg Gly Glu Val Gln Ala Met Leu
    130                 135                 140
Gly Gln Ser Thr Glu Glu Leu Arg Val Arg Leu Ala Ser His Leu Arg
145                 150                 155                 160
Lys Leu Arg Lys Arg Leu Leu Arg Asp Ala Asp Asp Leu Gln Lys Arg
                165                 170                 175
Leu Ala Val Tyr Gln Ala Gly Ala Arg Glu Gly Ala Glu Arg Gly Leu
            180                 185                 190
Ser Ala Ile Arg Glu Arg Leu Gly Pro Leu Val Glu Gln Gly Arg Val
        195                 200                 205
Arg Ala Ala Thr Val Gly Ser Leu Ala Gly Gln Pro Leu Gln Glu Arg
    210                 215                 220
Ala Gln Ala Trp Gly Glu Arg Leu Arg Ala Arg Met Glu Glu Met Gly
225                 230                 235                 240
Ser Arg Thr Arg Asp Arg Leu Asp Glu Val Lys Glu Gln Val Ala Glu
                245                 250                 255
Val Arg Ala Lys Leu Glu Glu Gln Ala Gln Gln Ile Arg Leu Gln Ala
            260                 265                 270
Glu Ala Phe Gln Ala Arg Leu Lys Ser Trp Phe Glu Pro Leu Val Glu
        275                 280                 285
Asp Met Gln Arg Gln Trp Ala Gly Leu Val Glu Lys Val Gln Ala Ala
    290                 295                 300
Val Gly Thr Ser Ala Ala Pro Val Pro Ser Asp Asn His
305                 310                 315
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<210> 65
<211> 2493

<212> DNA
<213> Homo sapiens

<400> 65
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cccatccctc agaagttatt tggggaggtg acttcccctc tgttccccaa gccttacccc     180
aacaactttg aaacaaccac tgtgatcaca gtccccacgg gatacagggt gaagctcgtc     240
ttccagcagt ttgacctgga gccttctgaa ggctgcttct atgattatgt caagatctct     300
gctgataaga aaagcctggg gaggttctgt gggcaactgg gttctccact gggcaacccc     360
ccgggaaaga aggaatttat gtcccaaggg aacaagatgc tgctgacctt ccacacagac     420
ttctccaacg aggagaatgg gaccatcatg ttctacaagg gcttcctggc ctactaccaa     480
gctgtggacc ttgatgaatg tgcttcccgg agcaaatcag gggaggagga tccccagccc     540
cagtgccagc acctgtgtca caactacgtt ggaggctact tctgttcctg ccgtccaggc     600
tatgagcttc aggaagacag gcattcctgc caggctgagt gcagcagcga gctgtacacg     660
gaggcatcag gctacatctc cagcctggag taccctcggt cctacccccc tgacctgcgc     720
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caaggctacc agctcataga ggggaaccag gtgctgcatt ccttcacagc tgtctgccag    1140
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tgtgagaact ggctccgggg aaagaatagg atggatgtgt tctctcaaaa catgttctgt    1980
gctggacacc catctctaaa gcaggacgcc tgccaggggg atagtggggg cgtttttgca    2040
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<210> 66
<211> 705
<212> PRT
<213> Homo sapiens

<400> 66
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Met Trp Leu Leu Tyr Leu Leu Val Pro Ala Leu Phe Cys Arg Ala Gly
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Gly Ser Ile Pro Ile Pro Gln Lys Leu Phe Gly Glu Val Thr Ser Pro
            20                  25                  30
Leu Phe Pro Lys Pro Tyr Pro Asn Asn Phe Glu Thr Thr Thr Val Ile
        35                  40                  45
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Thr Val Pro Thr Gly Tyr Arg Val Lys Leu Val Phe Gln Gln Phe Asp
    50                  55                  60
Leu Glu Pro Ser Glu Gly Cys Phe Tyr Asp Tyr Val Lys Ile Ser Ala
65                  70                  75                  80
Asp Lys Lys Ser Leu Gly Arg Phe Cys Gly Gln Leu Gly Ser Pro Leu
                85                  90                  95
Gly Asn Pro Pro Gly Lys Lys Glu Phe Met Ser Gln Gly Asn Lys Met
            100                 105                 110
Leu Leu Thr Phe His Thr Asp Phe Ser Asn Glu Glu Asn Gly Thr Ile
        115                 120                 125
Met Phe Tyr Lys Gly Phe Leu Ala Tyr Tyr Gln Ala Val Asp Leu Asp
    130                 135                 140
Glu Cys Ala Ser Arg Ser Lys Ser Gly Glu Glu Asp Pro Gln Pro Gln
145                 150                 155                 160
Cys Gln His Leu Cys His Asn Tyr Val Gly Gly Tyr Phe Cys Ser Cys
                165                 170                 175
Arg Pro Gly Tyr Glu Leu Gln Glu Asp Arg His Ser Cys Gln Ala Glu
            180                 185                 190
Cys Ser Ser Glu Leu Tyr Thr Glu Ala Ser Gly Tyr Ile Ser Ser Leu
        195                 200                 205
Glu Tyr Pro Arg Ser Tyr Pro Pro Asp Leu Arg Cys Asn Tyr Ser Ile
    210                 215                 220
Arg Val Glu Arg Gly Leu Thr Leu His Leu Lys Phe Leu Glu Pro Phe
225                 230                 235                 240
Asp Ile Asp Asp His Gln Gln Val His Cys Pro Tyr Asp Gln Leu Gln
                245                 250                 255
Ile Tyr Ala Asn Gly Lys Asn Ile Gly Glu Phe Cys Gly Lys Gln Arg
            260                 265                 270
Pro Pro Asp Leu Asp Thr Ser Ser Asn Ala Val Asp Leu Leu Phe Phe
        275                 280                 285
Thr Asp Glu Ser Gly Asp Ser Arg Gly Trp Lys Leu Arg Tyr Thr Thr
    290                 295                 300
Glu Ile Ile Lys Cys Pro Gln Pro Lys Thr Leu Asp Glu Phe Thr Ile
305                 310                 315                 320
Ile Gln Asn Leu Gln Pro Gln Tyr Gln Phe Arg Asp Tyr Phe Ile Ala
                325                 330                 335
Thr Cys Lys Gln Gly Tyr Gln Leu Ile Glu Gly Asn Gln Val Leu His
            340                 345                 350
Ser Phe Thr Ala Val Cys Gln Asp Asp Gly Thr Trp His Arg Ala Met
        355                 360                 365
Pro Arg Cys Lys Ile Lys Asp Cys Gly Gln Pro Arg Asn Leu Pro Asn
    370                 375                 380
Gly Asp Phe Arg Tyr Thr Thr Thr Met Gly Val Asn Thr Tyr Lys Ala
385                 390                 395                 400
Arg Ile Gln Tyr Tyr Cys His Glu Pro Tyr Tyr Lys Met Gln Thr Arg
                405                 410                 415
Ala Gly Ser Arg Glu Ser Glu Gln Gly Val Tyr Thr Cys Thr Ala Gln
            420                 425                 430
Gly Ile Trp Lys Asn Glu Gln Lys Gly Glu Lys Ile Pro Arg Cys Leu
        435                 440                 445
Pro Val Cys Gly Lys Pro Val Asn Pro Val Glu Gln Arg Gln Arg Ile
    450                 455                 460
Ile Gly Gly Gln Lys Ala Lys Met Gly Asn Phe Pro Trp Gln Val Phe
465                 470                 475                 480
Thr Asn Ile His Gly Arg Gly Gly Gly Ala Leu Leu Gly Asp Arg Trp
                485                 490                 495
Ile Leu Thr Ala Ala His Thr Leu Tyr Pro Lys Glu His Glu Ala Gln
            500                 505                 510
Ser Asn Ala Ser Leu Asp Val Phe Leu Gly His Thr Asn Val Glu Glu
        515                 520                 525
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Leu Met Lys Leu Gly Asn His Pro Ile Arg Arg Val Ser Val His Pro
530 535 540
Asp Tyr Arg Gln Asp Glu Ser Tyr Asn Phe Glu Gly Asp Ile Ala Leu
545 550 555 560
Leu Glu Leu Glu Asn Ser Val Thr Leu Gly Pro Asn Leu Leu Pro Ile
565 570 575
Cys Leu Pro Asp Asn Asp Thr Phe Tyr Asp Leu Gly Leu Met Gly Tyr
580 585 590
Val Ser Gly Phe Gly Val Met Glu Glu Lys Ile Ala His Asp Leu Arg
595 600 605
Phe Val Arg Leu Pro Val Ala Asn Pro Gln Ala Cys Glu Asn Trp Leu
610 615 620
Arg Gly Lys Asn Arg Met Asp Val Phe Ser Gln Asn Met Phe Cys Ala
625 630 635 640
Gly His Pro Ser Leu Lys Gln Asp Ala Cys Gln Gly Asp Ser Gly Gly
645 650 655
Val Phe Ala Val Arg Asp Pro Asn Thr Asp Arg Trp Val Ala Thr Gly
660 665 670
Ile Val Ser Trp Gly Ile Gly Cys Ser Arg Gly Tyr Gly Phe Tyr Thr
675 680 685
Lys Val Leu Asn Tyr Val Asp Trp Ile Lys Lys Glu Met Glu Glu Glu
690 695 700
Asp
705

<210> 67
<211> 777
<212> DNA
<213> Homo sapiens

<400> 67
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<210> 68
<211> 130
<212> PRT
<213> Homo sapiens

<400> 68
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Thr Cys Ser Gly Val Glu Ala Gly Lys Lys Lys Cys Ser Glu Ser Ser
20 25 30
Asp Ser Gly Ser Gly Phe Trp Lys Ala Leu Thr Phe Met Ala Val Gly
35 40 45
Gly Gly Leu Ala Val Ala Gly Leu Pro Ala Leu Gly Phe Thr Gly Ala
50 55 60

Gly Ile Ala Ala Asn Ser Val Ala Ala Ser Leu Met Ser Trp Ser Ala
65 70 75 80
Ile Leu Asn Gly Gly Gly Val Pro Ala Gly Gly Leu Val Ala Thr Leu
85 90 95
Gln Ser Leu Gly Ala Gly Gly Ser Ser Val Val Ile Gly Asn Ile Gly
100 105 110
Ala Leu Met Arg Tyr Ala Thr His Lys Tyr Leu Asp Ser Glu Glu Asp
115 120 125
Glu Glu
130

<210> 69
<211> 2402
<212> DNA
<213> Homo sapiens

<400> 69
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tc 2402

<210> 70

<211> 628
<212> PRT
<213> Homo sapiens

<400> 70
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20 25 30
Val Arg Leu Ser Val Pro Pro Leu Val Glu Val Met Arg Gly Lys Ser
35 40 45
Val Ile Leu Asp Cys Thr Pro Thr Gly Thr His Asp His Tyr Met Leu
50 55 60
Glu Trp Phe Leu Thr Asp Arg Ser Gly Ala Arg Pro Arg Leu Ala Ser
65 70 75 80
Ala Glu Met Gln Gly Ser Glu Leu Gln Val Thr Met His Asp Thr Arg
85 90 95
Gly Arg Ser Pro Pro Tyr Gln Leu Asp Ser Gln Gly Arg Leu Val Leu
100 105 110
Ala Glu Ala Gln Val Gly Asp Glu Arg Asp Tyr Val Cys Val Val Arg
115 120 125
Ala Gly Ala Ala Gly Thr Ala Glu Ala Thr Ala Arg Leu Asn Val Phe
130 135 140
Ala Lys Pro Glu Ala Thr Glu Val Ser Pro Asn Lys Gly Thr Leu Ser
145 150 155 160
Val Met Glu Asp Ser Ala Gln Glu Ile Ala Thr Cys Asn Ser Arg Asn
165 170 175
Gly Asn Pro Ala Pro Lys Ile Thr Trp Tyr Arg Asn Gly Gln Arg Leu
180 185 190
Glu Val Pro Val Glu Met Asn Pro Glu Gly Tyr Met Thr Ser Arg Thr
195 200 205
Val Arg Glu Ala Ser Gly Leu Leu Ser Leu Thr Ser Thr Leu Tyr Leu
210 215 220
Arg Leu Arg Lys Asp Asp Arg Asp Ala Ser Phe His Cys Ala Ala His
225 230 235 240
Tyr Ser Leu Pro Glu Gly Arg His Gly Arg Leu Asp Ser Pro Thr Phe
245 250 255
His Leu Thr Leu His Tyr Pro Thr Glu His Val Gln Phe Trp Val Gly
260 265 270
Ser Pro Ser Thr Pro Ala Gly Trp Val Arg Glu Gly Asp Thr Val Gln
275 280 285
Leu Leu Cys Arg Gly Asp Gly Ser Pro Ser Pro Glu Tyr Thr Leu Phe
290 295 300
Arg Leu Gln Asp Glu Gln Glu Glu Val Leu Asn Val Asn Leu Glu Gly
305 310 315 320
Asn Leu Thr Leu Glu Gly Val Thr Arg Gly Gln Ser Gly Thr Tyr Gly
325 330 335
Cys Arg Val Glu Asp Tyr Asp Ala Ala Asp Asp Val Gln Leu Ser Lys
340 345 350
Thr Leu Glu Leu Arg Val Ala Tyr Leu Asp Pro Leu Glu Leu Ser Glu
355 360 365
Gly Lys Val Leu Ser Leu Pro Leu Asn Ser Ser Ala Val Val Asn Cys
370 375 380
Ser Val His Gly Leu Pro Thr Pro Ala Leu Arg Trp Thr Lys Asp Ser
385 390 395 400
Thr Pro Leu Gly Asp Gly Pro Met Leu Ser Leu Ser Ser Ile Thr Phe
405 410 415
Asp Ser Asn Gly Thr Tyr Val Cys Glu Ala Ser Leu Pro Thr Val Pro
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Val Leu Ser Arg Thr Gln Asn Phe Thr Leu Leu Val Gln Gly Ser Pro
435 440 445
Glu Leu Lys Thr Ala Glu Ile Glu Pro Lys Ala Asp Gly Ser Trp Arg
450 455 460
Glu Gly Asp Glu Val Thr Leu Ile Cys Ser Ala Arg Gly His Pro Asp
465 470 475 480
Pro Lys Leu Ser Trp Ser Gln Leu Gly Gly Ser Pro Ala Glu Pro Ile
485 490 495
Pro Gly Arg Gln Gly Trp Val Ser Ser Ser Leu Thr Leu Lys Val Thr
500 505 510
Ser Ala Leu Ser Arg Asp Gly Ile Ser Cys Glu Ala Ser Asn Pro His
515 520 525
Gly Asn Lys Arg His Val Phe His Phe Gly Ala Val Ser Pro Gln Thr
530 535 540
Ser Gln Ala Gly Val Ala Val Met Ala Val Ala Val Ser Val Gly Leu
545 550 555 560
Leu Leu Leu Val Val Ala Val Phe Tyr Cys Val Arg Arg Lys Gly Gly
565 570 575
Pro Cys Cys Arg Gln Arg Arg Glu Lys Gly Ala Pro Pro Pro Gly Glu
580 585 590
Pro Gly Leu Ser His Ser Gly Ser Glu Gln Pro Glu Gln Thr Gly Leu
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Gly Asp Glu Cys
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<210> 71
<211> 5460
<212> DNA
<213> Homo sapiens

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<211> 1466
<212> PRT
<213> Homo sapiens

<400> 72
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Ser His Leu Gly Gln Ser Tyr Ala Asp Arg Asp Val Trp Lys Pro Glu
35 40 45
Pro Cys Gln Ile Cys Val Cys Asp Ser Gly Ser Val Leu Cys Asp Asp
50 55 60
Ile Ile Cys Asp Asp Gln Glu Leu Asp Cys Pro Asn Pro Glu Ile Pro
65 70 75 80
Phe Gly Glu Cys Cys Ala Val Cys Pro Gln Pro Pro Thr Ala Pro Thr
85 90 95
Arg Pro Pro Asn Gly Gln Gly Pro Gln Gly Pro Lys Gly Asp Pro Gly
100 105 110
Pro Pro Gly Ile Pro Gly Arg Asn Gly Asp Pro Gly Ile Pro Gly Gln
115 120 125
Pro Gly Ser Pro Gly Ser Pro Gly Pro Pro Gly Ile Cys Glu Ser Cys
130 135 140
Pro Thr Gly Pro Gln Asn Tyr Ser Pro Gln Tyr Asp Ser Tyr Asp Val
145 150 155 160
Lys Ser Gly Val Ala Val Gly Gly Leu Ala Gly Tyr Pro Gly Pro Ala
165 170 175
Gly Pro Pro Gly Pro Pro Gly Pro Pro Gly Thr Ser Gly His Pro Gly
180 185 190
Ser Pro Gly Ser Pro Gly Tyr Gln Gly Pro Pro Gly Glu Pro Gly Gln
195 200 205
Ala Gly Pro Ser Gly Pro Pro Gly Pro Pro Gly Ala Ile Gly Pro Ser
210 215 220
Gly Pro Ala Gly Lys Asp Gly Glu Ser Gly Arg Pro Gly Arg Pro Gly
225 230 235 240
Glu Arg Gly Leu Pro Gly Pro Pro Gly Ile Lys Gly Pro Ala Gly Ile
245 250 255
Pro Gly Phe Pro Gly Met Lys Gly His Arg Gly Phe Asp Gly Arg Asn
260 265 270
Gly Glu Lys Gly Glu Thr Gly Ala Pro Gly Leu Lys Gly Glu Asn Gly
275 280 285
Leu Pro Gly Glu Asn Gly Ala Pro Gly Pro Met Gly Pro Arg Gly Ala
290 295 300
Pro Gly Glu Arg Gly Arg Pro Gly Leu Pro Gly Ala Ala Gly Ala Arg
305 310 315 320
Gly Asn Asp Gly Ala Arg Gly Ser Asp Gly Gln Pro Gly Pro Pro Gly
325 330 335
Pro Pro Gly Thr Ala Gly Phe Pro Gly Ser Pro Gly Ala Lys Gly Glu
340 345 350
Val Gly Pro Ala Gly Ser Pro Gly Ser Asn Gly Ala Pro Gly Gln Arg
355 360 365

Gly Glu Pro Gly Pro Gln Gly His Ala Gly Ala Gln Gly Pro Pro Gly
370 375 380
Pro Pro Gly Ile Asn Gly Ser Pro Gly Gly Lys Gly Glu Met Gly Pro
385 390 395 400
Ala Gly Ile Pro Gly Ala Pro Gly Leu Met Gly Ala Arg Gly Pro Pro
405 410 415
Gly Pro Ala Gly Ala Asn Gly Ala Pro Gly Leu Arg Gly Gly Ala Gly
420 425 430
Glu Pro Gly Lys Asn Gly Ala Lys Gly Glu Pro Gly Pro Arg Gly Glu
435 440 445
Arg Gly Glu Ala Gly Ile Pro Gly Val Pro Gly Ala Lys Gly Glu Asp
450 455 460
Gly Lys Asp Gly Ser Pro Gly Glu Pro Gly Ala Asn Gly Leu Pro Gly
465 470 475 480
Ala Ala Gly Glu Arg Gly Ala Pro Gly Phe Arg Gly Pro Ala Gly Pro
485 490 495
Asn Gly Ile Pro Gly Glu Lys Gly Pro Ala Gly Glu Arg Gly Ala Pro
500 505 510
Gly Pro Ala Gly Pro Arg Gly Ala Ala Gly Glu Pro Gly Arg Asp Gly
515 520 525
Val Pro Gly Gly Pro Gly Met Arg Gly Met Pro Gly Ser Pro Gly Gly
530 535 540
Pro Gly Ser Asp Gly Lys Pro Gly Pro Pro Gly Ser Gln Gly Glu Ser
545 550 555 560
Gly Arg Pro Gly Pro Pro Gly Pro Ser Gly Pro Arg Gly Gln Pro Gly
565 570 575
Val Met Gly Phe Pro Gly Pro Lys Gly Asn Asp Gly Ala Pro Gly Lys
580 585 590
Asn Gly Glu Arg Gly Gly Pro Gly Gly Pro Gly Pro Gln Gly Pro Pro
595 600 605
Gly Lys Asn Gly Glu Thr Gly Pro Gln Gly Pro Pro Gly Pro Thr Gly
610 615 620
Pro Gly Gly Asp Lys Gly Asp Thr Gly Pro Pro Gly Pro Gln Gly Leu
625 630 635 640
Gln Gly Leu Pro Gly Thr Gly Gly Pro Pro Gly Glu Asn Gly Lys Pro
645 650 655
Gly Glu Pro Gly Pro Lys Gly Asp Ala Gly Ala Pro Gly Ala Pro Gly
660 665 670
Gly Lys Gly Asp Ala Gly Ala Pro Gly Glu Arg Gly Pro Pro Gly Leu
675 680 685
Ala Gly Ala Pro Gly Leu Arg Gly Gly Ala Gly Pro Pro Gly Pro Glu
690 695 700
Gly Gly Lys Gly Ala Ala Gly Pro Pro Gly Pro Pro Gly Ala Ala Gly
705 710 715 720
Thr Pro Gly Leu Gln Gly Met Pro Gly Glu Arg Gly Gly Leu Gly Ser
725 730 735
Pro Gly Pro Lys Gly Asp Lys Gly Glu Pro Gly Gly Pro Gly Ala Asp
740 745 750
Gly Val Pro Gly Lys Asp Gly Pro Arg Gly Pro Thr Gly Pro Ile Gly
755 760 765
Pro Pro Gly Pro Ala Gly Gln Pro Gly Asp Lys Gly Glu Gly Gly Ala
770 775 780
Pro Gly Leu Pro Gly Ile Ala Gly Pro Arg Gly Ser Pro Gly Glu Arg
785 790 795 800
Gly Glu Thr Gly Pro Pro Gly Pro Ala Gly Phe Pro Gly Ala Pro Gly
805 810 815
Gln Asn Gly Glu Pro Gly Gly Lys Gly Glu Arg Gly Ala Pro Gly Glu
820 825 830
Lys Gly Glu Gly Gly Pro Pro Gly Val Ala Gly Pro Pro Gly Gly Ser
835 840 845

Gly Pro Ala Gly Pro Pro Gly Pro Gln Gly Val Lys Gly Glu Arg Gly
850 855 860
Ser Pro Gly Gly Pro Gly Ala Ala Gly Phe Pro Gly Ala Arg Gly Leu
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Pro Gly Pro Pro Gly Ser Asn Gly Asn Pro Gly Pro Pro Gly Pro Ser
885 890 895
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900 905 910
Ala Pro Gly Ser Pro Gly Val Ser Gly Pro Lys Gly Asp Ala Gly Gln
915 920 925
Pro Gly Glu Lys Gly Ser Pro Gly Ala Gln Gly Pro Pro Gly Ala Pro
930 935 940
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945 950 955 960
Pro Pro Gly Met Pro Gly Pro Arg Gly Ser Pro Gly Pro Gln Gly Val
965 970 975
Lys Gly Glu Ser Gly Lys Pro Gly Ala Asn Gly Leu Ser Gly Glu Arg
980 985 990
Gly Pro Pro Gly Pro Gln Gly Leu Pro Gly Leu Ala Gly Thr Ala Gly
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Glu Pro Gly Arg Asp Gly Asn Pro Gly Ser Asp Gly Leu Pro Gly Arg
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1075 1080 1085
Gly Pro Arg Gly Asp Lys Gly Glu Thr Gly Glu Arg Gly Ala Ala Gly
1090 1095 1100
Ile Lys Gly His Arg Gly Phe Pro Gly Asn Pro Gly Ala Pro Gly Ser
1105 1110 1115 1120
Pro Gly Pro Ala Gly Gln Gln Gly Ala Ile Gly Ser Pro Gly Pro Ala
1125 1130 1135
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1140 1145 1150
Thr Ser Gly His Pro Gly Pro Ile Gly Pro Pro Gly Pro Arg Gly Asn
1155 1160 1165
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1170 1175 1180
Gly Pro Pro Gly Pro Pro Gly Ala Pro Gly Pro Cys Cys Gly Gly Val
1185 1190 1195 1200
Gly Ala Ala Ala Ile Ala Gly Ile Gly Gly Glu Lys Ala Gly Gly Phe
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Ala Pro Tyr Tyr Gly Asp Glu Pro Met Asp Phe Lys Ile Asn Thr Asp
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Glu Ile Met Thr Ser Leu Lys Ser Val Asn Gly Gln Ile Glu Ser Leu
1235 1240 1245
Ile Ser Pro Asp Gly Ser Arg Lys Asn Pro Ala Arg Asn Cys Arg Asp
1250 1255 1260
Leu Lys Phe Cys His Pro Glu Leu Lys Ser Gly Glu Tyr Trp Val Asp
1265 1270 1275 1280
Pro Asn Gln Gly Cys Lys Leu Asp Ala Ile Lys Val Phe Cys Asn Met
1285 1290 1295
Glu Thr Gly Glu Thr Cys Ile Ser Ala Asn Pro Leu Asn Val Pro Arg
1300 1305 1310
Lys His Trp Trp Thr Asp Ser Ser Ala Glu Lys Lys His Val Trp Phe
1315 1320 1325

Gly Glu Ser Met Asp Gly Gly Phe Gln Phe Ser Tyr Gly Asn Pro Glu
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Leu Pro Glu Asp Val Leu Asp Val Gln Leu Ala Phe Leu Arg Leu Leu
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                1365   1370   1375
Ala Tyr Met Asp Gln Ala Ser Gly Asn Val Lys Lys Ala Leu Lys Leu
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Met Gly Ser Asn Glu Gly Glu Phe Lys Ala Glu Gly Asn Ser Lys Phe
        1395   1400   1405
Thr Tyr Thr Val Leu Glu Asp Gly Cys Thr Lys His Thr Gly Glu Trp
    1410   1415   1420
Ser Lys Thr Val Phe Glu Tyr Arg Thr Arg Lys Ala Val Arg Leu Pro
1425   1430   1435   1440
Ile Val Asp Ile Ala Pro Tyr Asp Ile Gly Gly Pro Asp Gln Glu Phe
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<211> 1051
<212> DNA
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<210> 74
<211> 153
<212> PRT
<213> Homo sapiens

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Phe Gly Gly Leu Val Trp Ile Leu Val Ala Ser Ser Leu Val Pro Trp
        35   40   45
Pro Leu Val Gln Gly Trp Val Met Phe Val Ser Val Phe Cys Phe Val
    50   55   60
Ala Thr Thr Thr Leu Ile Ile Leu Tyr Ile Ile Gly Ala His Gly Gly
65   70   75   80

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Leu Phe Tyr Leu Ser Ala Ser Val Leu Glu Ala Leu Ala Thr Ile Thr
            100                 105                 110
Met Gln Asp Gly Phe Thr Tyr Arg His Tyr His Glu Asn Ile Ala Ala
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Val Val Phe Ser Tyr Ile Ala Thr Leu Leu Tyr Val Val His Ala Val
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Phe Ser Leu Ile Arg Trp Lys Ser Ser
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<211> 5416
<212> DNA
<213> Homo sapiens

<400> 75

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<211> 1366
<212> PRT
<213> Homo sapiens

<400> 76
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35 40 45
Pro Pro Gly Arg Asp Gly Glu Asp Gly Pro Thr Gly Pro Pro Gly Pro
50 55 60
Pro Gly Pro Pro Gly Pro Pro Gly Leu Gly Gly Asn Phe Ala Ala Gln
65 70 75 80
Tyr Asp Gly Lys Gly Val Gly Leu Gly Pro Gly Pro Met Gly Leu Met
85 90 95
Gly Pro Arg Gly Pro Pro Gly Ala Ala Gly Ala Pro Gly Pro Gln Gly
100 105 110
Phe Gln Gly Pro Ala Gly Glu Pro Gly Glu Pro Gly Gln Thr Gly Pro
115 120 125
Ala Gly Ala Arg Gly Pro Ala Gly Pro Pro Gly Lys Ala Gly Glu Asp
130 135 140
Gly His Pro Gly Lys Pro Gly Arg Pro Gly Glu Arg Gly Val Val Gly
145 150 155 160
Pro Gln Gly Ala Arg Gly Phe Pro Gly Thr Pro Gly Leu Pro Gly Phe
165 170 175
Lys Gly Ile Arg Gly His Asn Gly Leu Asp Gly Leu Lys Gly Gln Pro
180 185 190
Gly Ala Pro Gly Val Lys Gly Glu Pro Gly Ala Pro Gly Glu Asn Gly
195 200 205
Thr Pro Gly Gln Thr Gly Ala Arg Gly Leu Pro Gly Glu Arg Gly Arg
210 215 220
Val Gly Ala Pro Gly Pro Ala Gly Ala Arg Gly Ser Asp Gly Ser Val
225 230 235 240
Gly Pro Val Gly Pro Ala Gly Pro Asn Gly Ser Ala Gly Pro Pro Gly
245 250 255
Phe Pro Gly Ala Pro Gly Pro Lys Gly Glu Ile Gly Ala Val Gly Asn
260 265 270
Ala Gly Pro Thr Gly Pro Ala Gly Pro Arg Gly Glu Val Gly Leu Pro
275 280 285
Gly Leu Ser Gly Pro Val Gly Pro Pro Gly Asn Pro Gly Ala Asn Gly
290 295 300
Leu Thr Gly Ala Lys Gly Ala Ala Gly Leu Pro Gly Val Ala Gly Ala
305 310 315 320
Pro Gly Leu Pro Gly Pro Arg Gly Ile Pro Gly Pro Pro Gly Ala Ala
325 330 335
Gly Thr Thr Gly Ala Arg Gly Leu Val Gly Glu Pro Gly Pro Ala Gly
340 345 350
Ser Lys Gly Glu Ser Gly Asn Lys Gly Glu Pro Gly Ser Ala Gly Pro
355 360 365
Gln Gly Pro Pro Gly Pro Ser Gly Glu Glu Gly Lys Arg Gly Pro Asn
370 375 380
Gly Glu Ala Gly Ser Ala Gly Pro Pro Gly Pro Pro Gly Leu Arg Gly
385 390 395 400
Ser Pro Gly Ser Arg Gly Leu Pro Gly Ala Asp Gly Arg Ala Gly Val
405 410 415
Met Gly Pro Pro Gly Ser Arg Gly Ala Ser Gly Pro Ala Gly Val Arg
420 425 430
Gly Pro Asn Gly Asp Ala Gly Arg Pro Gly Glu Pro Gly Leu Met Gly
435 440 445
Pro Arg Gly Leu Pro Gly Ser Pro Gly Asn Ile Gly Pro Ala Gly Lys
450 455 460
Glu Gly Pro Val Gly Leu Pro Gly Ile Asp Gly Arg Pro Gly Pro Ile
465 470 475 480
Gly Pro Val Gly Ala Arg Gly Glu Pro Gly Asn Ile Gly Phe Pro Gly
485 490 495

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Ala Gly Leu Ala Gly Ala Arg Gly Ala Pro Gly Pro Asp Gly Asn Asn
        515                 520                 525
Gly Ala Gln Gly Pro Pro Gly Pro Gln Gly Val Gln Gly Gly Lys Gly
    530                 535                 540
Glu Gln Gly Pro Ala Gly Pro Pro Gly Phe Gln Gly Leu Pro Gly Pro
545                 550                 555                 560
Ser Gly Pro Ala Gly Glu Val Gly Lys Pro Gly Glu Arg Gly Leu His
                565                 570                 575
Gly Glu Phe Gly Leu Pro Gly Pro Ala Gly Pro Arg Gly Glu Arg Gly
            580                 585                 590
Pro Pro Gly Glu Ser Gly Ala Ala Gly Pro Thr Gly Pro Ile Gly Ser
        595                 600                 605
Arg Gly Pro Ser Gly Pro Pro Gly Pro Asp Gly Asn Lys Gly Glu Pro
    610                 615                 620
Gly Val Val Gly Ala Val Gly Thr Ala Gly Pro Ser Gly Pro Ser Gly
625                 630                 635                 640
Leu Pro Gly Glu Arg Gly Ala Ala Gly Ile Pro Gly Gly Lys Gly Glu
                645                 650                 655
Lys Gly Glu Pro Gly Leu Arg Gly Glu Ile Gly Asn Pro Gly Arg Asp
            660                 665                 670
Gly Ala Arg Gly Ala His Gly Ala Val Gly Ala Pro Gly Pro Ala Gly
        675                 680                 685
Ala Thr Gly Asp Arg Gly Glu Ala Gly Ala Ala Gly Pro Ala Gly Pro
    690                 695                 700
Ala Gly Pro Arg Gly Ser Pro Gly Glu Arg Gly Glu Val Gly Pro Ala
705                 710                 715                 720
Gly Pro Asn Gly Phe Ala Gly Pro Ala Gly Ala Ala Gly Gln Pro Gly
                725                 730                 735
Ala Lys Gly Glu Arg Gly Gly Lys Gly Pro Lys Gly Glu Asn Gly Val
            740                 745                 750
Val Gly Pro Thr Gly Pro Val Gly Ala Ala Gly Pro Ala Gly Pro Asn
        755                 760                 765
Gly Pro Pro Gly Pro Ala Gly Ser Arg Gly Asp Gly Gly Pro Pro Gly
    770                 775                 780
Met Thr Gly Phe Pro Gly Ala Ala Gly Arg Thr Gly Pro Pro Gly Pro
785                 790                 795                 800
Ser Gly Ile Ser Gly Pro Pro Gly Pro Pro Gly Pro Ala Gly Lys Glu
                805                 810                 815
Gly Leu Arg Gly Pro Arg Gly Asp Gln Gly Pro Val Gly Arg Thr Gly
            820                 825                 830
Glu Val Gly Ala Val Gly Pro Pro Gly Phe Ala Gly Glu Lys Gly Pro
        835                 840                 845
Ser Gly Glu Ala Gly Thr Ala Gly Pro Pro Gly Thr Pro Gly Pro Gln
    850                 855                 860
Gly Leu Leu Gly Ala Pro Gly Ile Leu Gly Leu Pro Gly Ser Arg Gly
865                 870                 875                 880
Glu Arg Gly Leu Pro Gly Val Ala Gly Ala Val Gly Glu Pro Gly Pro
                885                 890                 895
Leu Gly Ile Ala Gly Pro Pro Gly Ala Arg Gly Pro Pro Gly Ala Val
            900                 905                 910
Gly Ser Pro Gly Val Asn Gly Ala Pro Gly Glu Ala Gly Arg Asp Gly
        915                 920                 925
Asn Pro Gly Asn Asp Gly Pro Pro Gly Arg Asp Gly Gln Pro Gly His
    930                 935                 940
Lys Gly Glu Arg Gly Tyr Pro Gly Asn Ile Gly Pro Val Gly Ala Ala
945                 950                 955                 960
Gly Ala Pro Gly Pro His Gly Pro Val Gly Pro Ala Gly Lys His Gly
                965                 970                 975
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Asn Arg Gly Glu Thr Gly Pro Ser Gly Pro Val Gly Pro Ala Gly Ala
980 985 990
Val Gly Pro Arg Gly Pro Ser Gly Pro Gln Gly Ile Arg Gly Asp Lys
995 1000 1005
Gly Glu Pro Gly Glu Lys Gly Pro Arg Gly Leu Pro Gly Phe Lys Gly
1010 1015 1020
His Asn Gly Leu Gln Gly Leu Pro Gly Ile Ala Gly His His Gly Asp
1025 1030 1035 1040
Gln Gly Ala Pro Gly Ser Val Gly Pro Ala Gly Pro Arg Gly Pro Ala
1045 1050 1055
Gly Pro Ser Gly Pro Ala Gly Lys Asp Gly Arg Thr Gly His Pro Gly
1060 1065 1070
Thr Val Gly Pro Ala Gly Ile Arg Gly Pro Gln Gly His Gln Gly Pro
1075 1080 1085
Ala Gly Pro Pro Gly Pro Pro Gly Pro Pro Gly Pro Pro Gly Val Ser
1090 1095 1100
Gly Gly Gly Tyr Asp Phe Gly Tyr Asp Gly Asp Phe Tyr Arg Ala Asp
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Gln Pro Arg Ser Ala Pro Ser Leu Arg Pro Lys Asp Tyr Glu Val Asp
1125 1130 1135
Ala Thr Leu Lys Ser Leu Asn Asn Gln Ile Glu Thr Leu Leu Thr Pro
1140 1145 1150
Glu Gly Ser Arg Lys Asn Pro Ala Arg Thr Cys Arg Asp Leu Arg Leu
1155 1160 1165
Ser His Pro Glu Trp Ser Ser Gly Tyr Tyr Trp Ile Asp Pro Asn Gln
1170 1175 1180
Gly Cys Thr Met Glu Ala Ile Lys Val Tyr Cys Asp Phe Pro Thr Gly
1185 1190 1195 1200
Glu Thr Cys Ile Arg Ala Gln Pro Glu Asn Ile Pro Ala Lys Asn Trp
1205 1210 1215
Tyr Arg Ser Ser Lys Asp Lys Lys His Val Trp Leu Gly Glu Thr Ile
1220 1225 1230
Asn Ala Gly Ser Gln Phe Glu Tyr Asn Val Glu Gly Val Thr Ser Lys
1235 1240 1245
Glu Met Ala Thr Gln Leu Ala Phe Met Arg Leu Leu Ala Asn Tyr Ala
1250 1255 1260
Ser Gln Asn Ile Thr Tyr His Cys Lys Asn Ser Ile Ala Tyr Met Asp
1265 1270 1275 1280
Glu Glu Thr Gly Asn Leu Lys Lys Ala Val Ile Leu Gln Gly Ser Asn
1285 1290 1295
Asp Val Glu Leu Val Ala Glu Gly Asn Ser Arg Phe Thr Tyr Thr Val
1300 1305 1310
Leu Val Asp Gly Cys Ser Lys Lys Thr Asn Glu Trp Gly Lys Thr Ile
1315 1320 1325
Ile Glu Tyr Lys Thr Asn Lys Pro Ser Arg Leu Pro Phe Leu Asp Ile
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<211> 1082
<212> DNA
<213> Homo sapiens

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ttactgatgg tgctgctcac atctgtggtc cagggcaggg ccactccaga gaattacctt 180

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<211> 258
<212> PRT
<213> Homo sapiens

<400> 78
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Pro Glu Asn Tyr Leu Phe Gln Gly Arg Gln Glu Cys Tyr Ala Phe Asn
        35                  40                  45
Gly Thr Gln Arg Phe Leu Glu Arg Tyr Ile Tyr Asn Arg Glu Glu Phe
    50                  55                  60
Ala Arg Phe Asp Ser Asp Val Gly Glu Phe Arg Ala Val Thr Glu Leu
65                  70                  75                  80
Gly Arg Pro Ala Ala Glu Tyr Trp Asn Ser Gln Lys Asp Ile Leu Glu
                85                  90                  95
Glu Lys Arg Ala Val Pro Asp Arg Met Cys Arg His Asn Tyr Glu Leu
            100                 105                 110
Gly Gly Pro Met Thr Leu Gln Arg Arg Val Gln Pro Arg Val Asn Val
        115                 120                 125
Ser Pro Ser Lys Lys Gly Pro Leu Gln His His Asn Leu Leu Val Cys
    130                 135                 140
His Val Thr Asp Phe Tyr Pro Gly Ser Ile Gln Val Arg Trp Phe Leu
145                 150                 155                 160
Asn Gly Gln Glu Glu Thr Ala Gly Val Val Ser Thr Asn Leu Ile Arg
                165                 170                 175
Asn Gly Asp Trp Thr Phe Gln Ile Leu Val Met Leu Glu Met Thr Pro
            180                 185                 190
Gln Gln Gly Asp Val Tyr Thr Cys Gln Val Glu His Thr Ser Leu Asp
        195                 200                 205
Ser Pro Val Thr Val Glu Trp Lys Ala Gln Ser Asp Ser Ala Arg Ser
    210                 215                 220
Lys Thr Leu Thr Gly Ala Gly Gly Phe Val Leu Gly Leu Ile Ile Cys
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Ser Ala

<210> 79
<211> 996
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<212> DNA
<213> Homo sapiens

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aaaaaaaaaa aaaaaaaaaa aaagaattcc accaca 996

<210> 80
<211> 180
<212> PRT
<213> Homo sapiens

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Ile Ile Val Ile Leu Gly Val Pro Leu Ile Ile Phe Thr Ile Lys Ala
35 40 45
Asn Ser Glu Ala Cys Arg Asp Gly Leu Arg Ala Val Met Glu Cys Arg
50 55 60
Asn Val Thr His Leu Leu Gln Gln Glu Leu Thr Glu Ala Gln Lys Gly
65 70 75 80
Phe Gln Asp Val Glu Ala Gln Ala Ala Thr Cys Asn His Thr Val Met
85 90 95
Ala Leu Met Ala Ser Leu Asp Ala Glu Lys Ala Gln Gly Gln Lys Lys
100 105 110
Val Glu Glu Leu Glu Gly Glu Ile Thr Thr Leu Asn His Lys Leu Gln
115 120 125
Asp Ala Ser Ala Glu Val Glu Arg Leu Arg Arg Glu Asn Gln Val Leu
130 135 140
Ser Val Arg Ile Ala Asp Lys Lys Tyr Tyr Pro Ser Ser Gln Asp Ser
145 150 155 160
Ser Ser Ala Ala Ala Pro Gln Leu Leu Ile Val Leu Leu Gly Leu Ser
165 170 175
Ala Leu Leu Gln
180

<210> 81
<211> 4316
<212> DNA
<213> Homo sapiens

<400> 81
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65                  70                  75                  80
Trp Glu Trp Thr Thr Gly Tyr Ala Lys Ala Asn Ala Gln Thr Asp Arg
                85                  90                  95
Val Ala Leu Arg Asn Leu Leu Arg Arg Tyr Asn Gln Ser Glu Ala Gly
            100                 105                 110
Ser His Thr Leu Gln Gly Met Asn Gly Cys Asp Met Gly Pro Asp Gly
        115                 120                 125
Arg Leu Leu Arg Gly Tyr His Gln His Ala Tyr Asp Gly Lys Asp Tyr
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Ile Ser Leu Asn Glu Asp Leu Arg Ser Trp Thr Ala Ala Asp Thr Val
145                 150                 155                 160
Ala Gln Ile Thr Gln Arg Phe Tyr Glu Ala Glu Glu Tyr Ala Glu Glu
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Phe Arg Thr Tyr Leu Glu Gly Glu Cys Leu Glu Leu Leu Arg Arg Tyr
            180                 185                 190
Leu Glu Asn Gly Lys Glu Thr Leu Gln Arg Ala Asp Pro Pro Lys Ala
        195                 200                 205
His Val Ala His His Pro Ile Ser Asp His Glu Ala Thr Leu Arg Cys
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Trp Ala Leu Gly Phe Tyr Pro Ala Glu Ile Thr Leu Thr Trp Gln Arg
225                 230                 235                 240
Asp Gly Glu Glu Gln Thr Gln Asp Thr Glu Leu Val Glu Thr Arg Pro
                245                 250                 255
Ala Gly Asp Gly Thr Phe Gln Lys Trp Ala Ala Val Val Val Pro Ser
            260                 265                 270
Gly Glu Glu Gln Arg Tyr Thr Cys His Val Gln His Glu Gly Leu Pro
        275                 280                 285
Gln Pro Leu Ile Leu Arg Trp Glu Gln Ser Pro Gln Pro Thr Ile Pro
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Ile Val Gly Ile Val Ala Gly Leu Val Val Leu Gly Ala Val Val Thr
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Pro Gly Ala Lys Ser Ala Ala Gln Ala Ala Ala Gln Thr Asn Ser Asn
50 55 60
Ala Ala Gly Lys Gln Leu Arg Lys Glu Ser Gln Lys Asp Arg Lys Asn
65 70 75 80
Pro Leu Pro Pro Ser Val Gly Val Val Asp Lys Lys Glu Glu Thr Gln
85 90 95
Pro Pro Val Ala Leu Lys Lys Glu Gly Ile Arg Arg Val Gly Arg Arg
100 105 110
Pro Asp Gln Gln Leu Gln Gly Glu Gly Lys Ile Ile Asp Arg Arg Pro
115 120 125
Glu Arg Arg Pro Pro Arg Glu Arg Arg Phe Glu Lys Pro Leu Glu Glu
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Lys Gly Glu Gly Gly Glu Phe Ser Val Asp Arg Pro Ile Ile Asp Arg
145 150 155 160
Pro Ile Arg Gly Arg Gly Gly Leu Gly Arg Gly Arg Gly Gly Arg Gly
165 170 175

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Arg Gly Met Gly Arg Gly Asp Gly Phe Asp Ser Arg Gly Lys Arg Glu
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Phe Asp Arg His Ser Gly Ser Asp Arg Ser Ser Phe Ser His Tyr Ser
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Gly Leu Lys His Glu Asp Lys Arg Gly Gly Ser Gly Ser His Asn Trp
    210                 215                 220
Gly Thr Val Lys Asp Glu Leu Thr Glu Ser Pro Lys Tyr Ile Gln Lys
225                 230                 235                 240
Gln Ile Ser Tyr Asn Tyr Ser Asp Leu Asp Gln Ser Asn Val Thr Glu
                245                 250                 255
Glu Thr Pro Glu Gly Glu Glu His His Pro Val Ala Asp Thr Glu Asn
            260                 265                 270
Lys Glu Asn Glu Val Glu Glu Val Lys Glu Glu Gly Pro Lys Glu Met
        275                 280                 285
Thr Leu Asp Glu Trp Lys Ala Ile Gln Asn Lys Asp Arg Ala Lys Val
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Glu Phe Asn Ile Arg Lys Pro Asn Glu Gly Ala Asp Gly Gln Trp Lys
305                 310                 315                 320
Lys Gly Phe Val Leu His Lys Ser Lys Ser Glu Glu Ala His Ala Glu
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Asp Ser Val Met Asp His His Phe Arg Lys Pro Ala Asn Asp Ile Thr
            340                 345                 350
Ser Gln Leu Glu Ile Asn Phe Gly Asp Leu Gly Arg Pro Gly Arg Gly
        355                 360                 365
Gly Arg Gly Gly Arg Gly Gly Arg Gly Arg Gly Gly Arg Pro Asn Arg
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35 40 45
Val Arg Lys Ser Lys Arg Pro Val Phe Ser His Cys Gln Val Pro Glu
50 55 60
Thr Gln Lys Thr Asp Thr Arg His Leu Ser Gly Ala Arg Ala Gly Val
65 70 75 80
Cys Pro Cys Cys His Pro Asp Gly Leu Leu Ala Thr Met Arg Asp Leu
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Leu Gln Tyr Ile Ala Cys Phe Phe Ala Phe Phe Ser Ala Gly Phe Leu
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Ile Val Ala Thr Trp Thr Asp Cys Trp Met Val Asn Ala Asp Asp Ser
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Ala Glu His Pro Leu Lys Leu Val Val Thr Arg Ala Leu Met Ile Thr
165 170 175
Ala Asp Ile Leu Ala Gly Phe Gly Phe Leu Thr Leu Leu Leu Gly Leu
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Asp Cys Val Lys Phe Leu Pro Asp Glu Pro Tyr Ile Lys Val Arg Ile
195 200 205
Cys Phe Val Ala Gly Ala Thr Leu Leu Ile Ala Gly Thr Pro Gly Ile
210 215 220
Ile Gly Ser Val Trp Tyr Ala Val Asp Val Tyr Val Glu Arg Ser Thr
225 230 235 240
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245 250 255
Ser Cys Trp Leu Gly Met Ala Gly Ser Leu Gly Cys Phe Leu Ala Gly
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(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(63) Related by continuation (CON) or continuation-in-part (CIP) to earlier application:
US 60/194,336 (CIP)
Filed on 3 April 2000 (03.04.2000)

(71) Applicant *(for all designated States except US)*: THE GOVERNMENT OF THE UNITED STATES OF AMERICA, as represented by THE SECRETARY, DEPARTMENT OF HEALTH AND HUMAN SERVICES [US/US]; c/o National Institutes of Health, Office of Technology Transfer, 6011 Executive Boulevard, Suite 325, Rockville, MD 20852-3804 (US).

(72) Inventors; and
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(74) Agents: MILLER, Mary, L. et al.; Needle & Rosenberg, P.C., 127 Peachtree Street, N.E., Suite 1200, Atlanta, GA 30303-1811 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

(88) Date of publication of the international search report: 22 May 2003

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/075177 A3

(54) Title: TUMOR MARKERS IN OVARIAN CANCER

(57) Abstract: The present invention features methods of diagnosing and prognosticating ovarian tumors by detecting increased expression of an ovarian tumor marker gene in a subject or in a sample from a subject. Also featured are kits for the aforementioned diagnostic and prognostic methods. In addition, the invention features methods of treating and preventing ovarian tumors, and methods of inhibiting the growth or metastasis of ovarian tumors, by modulating the production or activity of an ovarian tumor marker polypeptide. Further featured are methods of inhibiting the growth or metastasis of an ovarian tumor by contacting an ovarian tumor cell with an antibody that specifically binds an ovarian tumor marker polypeptide.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 01/10947

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12Q1/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, CHEM ABS Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 53040 A (SCHMITT ARMIN ;SPECHT THOMAS (DE); DAHL EDGAR (DE); HINZMANN BERND) 21 October 1999 (1999-10-21) Tabelle I, SEQ ID NO:72 ---	1-22,28, 29,32

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
1 October 2002	10.01.2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Mata-Vicente, M

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International Application No
PCT/US 01/10947

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	HOUGH COLLEEN D ET AL: "Comparison of sage-generated expression profiles between ovarian cancer and human ovarian surface epithelium." PROCEEDINGS OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH ANNUAL, no. 41, March 2000 (2000-03), pages 310-311, XP008008525 91st Annual Meeting of the American Association for Cancer Research.;San Francisco, California, USA; April 01-05, 2000, March, 2000 ISSN: 0197-016X the whole document ---	
A	HOUGH C D ET AL: "Use of SAGE to study gene expression in ovarian cancer." PROCEEDINGS OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH ANNUAL, vol. 40, March 1999 (1999-03), page 34 XP008008524 90th Annual Meeting of the American Association for Cancer Research;Philadelphia, Pennsylvania, USA; April 10-14, 1999, March, 1999 ISSN: 0197-016X the whole document ---	
A	DEPASQUALE S E ET AL: "Differential expression of the pRb2 tumor suppressor gene in human epithelial ovarian carcinoma compared to ovarian tumors of low malignant potential and normal ovaries." PROCEEDINGS OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH ANNUAL, vol. 38, 1997, page 109 XP008008526 Eighty-eighth Annual Meeting of the American Association for Cancer Research;San Diego, California, USA; April 12-16, 1997, 1997 ISSN: 0197-016X the whole document ---	
A	MOK SAMUEL C ET AL: "Molecular Cloning of Differentially Expressed Genes in Human Epithelial Ovarian Cancer." GYNECOLOGIC ONCOLOGY, vol. 52, no. 2, 1994, pages 247-252, XP002128355 ISSN: 0090-8258 page 247, right-hand column, paragraph 1 page 248, right-hand column, last paragraph page 251, right-hand column ---	

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2

International Application No
PCT/US 01/10947

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,A	HOUGH COLLEEN D ET AL: "Large-scale serial analysis of gene expression reveals genes differentially expressed in ovarian cancer." CANCER RESEARCH, vol. 60, no. 22, 15 November 2000 (2000-11-15), pages 6281-6287, XP002215320 ISSN: 0008-5472 the whole document -----	

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 01/10947

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210

2. [X] Claims Nos.: 30
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [X] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
Claims (1-22, 28, 29 and 32) - partially; claim 30 - completely

Remark n Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Claim 6 and, as far as an "in vivo" method is concerned, claims 1-3, 7-13 and 19-21 and partially 22, 28 and 29 are directed to a diagnostic method practised on the human/animal body and the search has been carried out and based on the alleged effects of the compound/composition.

Claims 14-18 and partially claims 22, 28 and 29 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.2

Claims Nos.: 30

Claim 30 refers to an antibody without giving a true technical characterization. Moreover, no such compounds are defined in the application. In consequence, the scope of said claim is ambiguous and vague, and its subject-matter is not sufficiently disclosed and supported (Art. 5 and 6 PCT). No search can be carried out for purely speculative claims whose wording is, in fact, a mere recitation of the results to be achieved.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

International Application No. PCT/US 01/10947

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

Invention 1: Claims (1-22, 28, 29 and 32) - partially; claim 30 - completely

Methods for detecting/diagnosing ovarian cancer or the predisposal to develop it, as well as a method to determine the effectiveness of a treatment against ovarian cancer, all comprising measuring the expression of the alpha prothymosin gene (SEQ ID NO:1). Method of treating or preventing ovarian cancer comprising modulating production or activity of the polypeptide encoded thereby (SEQ ID NO:2). Kit comprising the polynucleotide of the invention.

Inventions 2-19: Claims (1-22, 25, 28, 29, 31, 32 and 35) - partially

Invention 2: Methods for detecting/diagnosing ovarian cancer or the predisposal to develop it, as well as a method to determine the effectiveness of a treatment against ovarian cancer, all comprising measuring the expression of the beta polypeptide 2-like G protein subunit 1 gene (SEQ ID NO:3) or its tag SEQ ID NO:84. Method of treating or preventing ovarian cancer comprising modulating production or activity of the polypeptide encoded thereby (SEQ ID NO:4). Kits comprising the polynucleotides of the invention.
Ibidem for inventions 3-19, but restricted to each one of the other markers mentioned in claims 22 and 32: Invention 3 refers to Lutheran blood group (B-CAM) (SEQ ID NOs:5, 6 and 85) ... invention 19 refers to eIF-2-associated p67 (SEQ ID NOs:38, 39 and 102).

Inventions 20-40: Claims (1-21, 23, 26, 28, 29, 31, 33 and 36) - partially

Invention 20: Methods for detecting/diagnosing ovarian cancer or the predisposal to develop it, as well as a method to determine the effectiveness of a treatment against ovarian cancer, all comprising measuring the expression of the HLA-DR alpha chain gene (SEQ ID NO:40) or its tag SEQ ID NO:103. Method of treating or preventing ovarian cancer comprising modulating production or activity of the polypeptide encoded thereby (SEQ ID NO:41). Kits comprising the polynucleotides of the invention.
Ibidem for inventions 21-40, but restricted to each one of the other markers mentioned in claims 23 and 33: Invention 21 refers to cysteine-rich protein 1 (SEQ ID NOs:42, 43 and 104) ... invention 40 refers to HLA-Cw (SEQ ID NOs:81, 82 and 129).

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Inventions 41-43: Claims (1-21, 24, 27-29, 31, 34 and 37) - partially

Invention 41: Methods for detecting/diagnosing ovarian cancer or the predisposal to develop it, as well as a method to determine the effectiveness of a treatment against ovarian cancer, all comprising measuring the expression of the HOST-3 (Claudin-16) gene (SEQ ID NO:141). Method of treating or preventing ovarian cancer comprising modulating production or activity of the polypeptide encoded thereby (SEQ ID NO:142). Kit comprising the polynucleotide of the invention.
Ibidem for inventions 42 and 43, but restricted to each one of the other markers mentioned in claims 24 and 34: Invention 42 refers to HOST-4 (SEQ ID NO:144) and invention 43 refers to HOST-5 (SEQ ID NOs:146 and 147).

Inventions 44-49: Claims (1-21, 26, 28, 29, 31 and 36) - partially

Invention 44: Methods for detecting/diagnosing ovarian cancer or the predisposal to develop it, as well as a method to determine the effectiveness of a treatment against ovarian cancer, all comprising measuring the expression of the gene tag SEQ ID NO:106. Method of treating or preventing ovarian cancer comprising modulating production or activity of the polypeptide encoded thereby. Kit comprising the polynucleotide of the invention.
Ibidem for inventions 45-49, but restricted to each one of the other tags mentioned in claims 26 and 36: Invention 45 refers to tag SEQ ID NO:107 ... invention 36 refers to tag SEQ ID NO:122.

Inventions 50-51: Claims (1-21, 27-29, 31 and 37) - partially

Invention 50: Methods for detecting/diagnosing ovarian cancer or the predisposal to develop it, as well as a method to determine the effectiveness of a treatment against ovarian cancer, all comprising measuring the expression of the gene tag SEQ ID NO:143. Method of treating or preventing ovarian cancer comprising modulating production or activity of the polypeptide encoded thereby. Kit comprising the polynucleotide of the invention.
Ibidem for invention 51, but restricted to the other tag mentioned in claims 27 and 37 (tag SEQ ID NO:145).

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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		WO 9953040 A2	21-10-1999
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